ASSOCIATIONS BETWEEN MENSTRUAL CYCLE AND HORMONAL CONTRACEPTION WITH SATIETY HORMONES AND FOOD INTAKE

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ABSTRACT

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Introduction. The ovarian steroid hormones estradiol and progesterone are potentially capable of affecting dietary intake, which is supported by the vast evidence showing that food intake peaks during the luteal phase and reaches its nadir at ovulation (Hirschberg et al. 2012). Appetite-regulating hormones leptin, ghrelin, and insulin, referred to as satiety hormones, may have interactions with estradiol and progesterone (Budak et al. 2006; Klok et al. 2007; Hirschberg 2012). The objective of this study was to investigate fluctuations in food intake and satiety hormones across the menstrual cycle or hormonal contraceptive use.

Methods. 25 women, of whom 16 had never used hormonal contraception (N-group, age 26.2±4.4, BMI 66.6±6.9) and 9 had used hormonal contraception at least one year (H-group, age 22.9±2.4, BMI 19.6±2.9), enrolled in the present study. Data related to dietary intake and cravings were collected with 3-day prospective food record over four phases of the menstrual cycle or hormonal contraceptive use, along with venous blood samples and body composition measurements. Phases of the menstrual cycle were determined by combining counting method with the detection of luteinizing hormone surge in urine (De Jonge 2019).

Results. There were no differences in energy or macronutrient intake or cravings between the phases of the menstrual cycle or hormonal contraceptive use. In the N-group. leptin was significantly higher at ovulation and during the luteal phase compared to the menstrual phase and the follicular phase ($p<0.05^*$). In both groups, cravings were reported more in those subjects with higher progesterone levels during the follicular phase or the withdrawal bleeding. Progesterone was positively associated with energy intake in the H-group during the second active phase ($r=0.68$, $p < 0.05$). Strong negative correlations were observed between leptin and protein intake during the luteal phase ($r=-0.71$, $p < 0.01$), and insulin and protein intake at ovulation ($r=-0.74$, $p < 0.01$).

Conclusions. Findings of the present study do not support the hypothesis of changing dietary intake across the menstrual cycle in recreationally active athletic women. Progesterone might contribute to higher prevalence of cravings, regardless of hormonal contraceptive use. Higher leptin during the latter half of the menstrual cycle may predict the optimal functioning of hypothalamic-pituitary-ovarian axis, and thereby, eumenorrhea. Given that the regulation of appetite and cyclical hormonal variations are influenced by the interaction of multiple factors, further research with multidisciplinary approach is warranted.

Key Words: food intake, satiety hormones, appetite regulation, cravings, menstrual cycle, hormonal contraception, female athletes

ABBREVIATIONS

AG	acylated ghrelin
AgRP	agouti-related peptide
ARC	arcuate nucleus
BMI	body mass index
CCK	cholecystokinin
EE	ethinyl estradiol
FSH	follicle-stimulating hormone
GnRH	gonadotropin-releasing hormone
HPO-axis	hypothalamic-pituitary-ovarian axis
IR	insulin receptor
LEP-R	leptin receptor
LH	luteinizing hormone
NPY	neuropeptide Y
Ob gene	obesity gene
POMC	proopiomelanocortin
UnAG	unacylated ghrelin

CONTENTS

1 INTRODUCTION

One of the most important biological rhythms in woman's life, the menstrual cycle, is characterized by regularly fluctuating concentrations of endogenous sex steroid hormones. Estrogen, progestins, androgens and their interactions have broad effects on several body systems and functions. (De Jonge et al. 2019, Constantini et al. 2005). In the past decades, awareness of how the menstrual cycle can provide information about health and energy balance has gradually broadened as the number of women participating in recreational physical activity and competitive sports has increased (Greydanus & Patel 2002; De Souza 2003; Constantini et al. 2005; Davis & Hackney 2017). Roughly half of the female athletes use hormonal contraception for different purposes, which further induces changes by adding exogenous synthetic hormones to equation (Constantini et al. 2005; Martin et al. 2018; Larsen et al. 2020). Much work on the potential adverse effects of the hormonal contraceptive use has been carried out, yet there are still gaps in understanding how different chemical formulations of contraceptives influence on the health of a female athlete (Burrows & Peters 2012).

A growing body of evidence suggests that food cravings and dietary intake increase in the luteal phase of the menstrual cycle (Hirschberg 2012). The effects of hormonal contraception on food intake, however, are contradictory, as some reports have found them to increase food intake while others do not report significant differences to non-users (Davidsen et al. 2007). In some studies, macronutrient intake has been shown to fluctuate as well (Dye & Blundell 1997; Gorczyga et al. 2016). Nevertheless, reported results have been divergent, and the physiology of these changes is poorly understood as food intake is constantly under the influence of neurochemical, hormonal, physiological and psychological factors (Hirscberg 2012).

Leptin, ghrelin and insulin play major roles in the hormonal control of appetite and food intake. Their appetite-regulating effects are mediated via specific neurons in the hypothalamus. (Hirschberg 2012.) Ghrelin is secreted from gastric mucosa in response to fasting to stimulate hunger (Cummings et al. 2001). Adipose-derived leptin and pancreatic insulin, by turn, act as appetite-inhibiting signals and have more significant roles in long-term energy homeostasis (Hirschberg 2012). They are secreted in proportion to the body fat and have interactive effects with other myriad satiation signals such as duodenal peptide cholecystokinin (CCK) and intestinal glucagon-like peptide-1 (GLP-1) (Woods & D'Alessio 2008). Given that leptin and ghrelin have also regulatory roles in maintaining reproductive capacity and initiating the

puberty, it is conceivable to assume that their concentrations across the menstrual cycle may fluctuate too (Budak et al. 2006; Klok et al. 2007; Hirschberg 2012). In addition, there is some evidence that carbohydrate metabolism and insulin sensitivity are impaired during the luteal phase of the menstrual cycle, but the mechanisms behind this impairment remain to be clarified (Diamond et al. 1989; Pulido & Salazar 1999, Bennal & Kerure 2013).

Studies related to the concentrations of satiety hormones across the menstrual cycle or hormonal contraceptive use and associations with food intake are limited and have not been dealt with in depth. This lack of research is partly due to the highly complex regulation system of food intake involving crosstalk between the peripheral and the central nervous system (Brunetti et al. 2005; Hirschberg 2012), and partly resulting from divergent and inconsistent study designs. The aim of this Master's Thesis is to investigate changes in self-reported energy and macronutrient intake while examining serum leptin, ghrelin, insulin and glucose concentrations, across the menstrual cycle in recreational female athletes using or not using hormonal contraceptives. Exploring these associations may give additional tools and information to female athletes and their coaches to understand and facilitate weight management across the menstrual cycle. Results can benefit passive individuals and be used to develop effective strategies for the prevention and treatment of wide-spreading obesity as well.

2 THE MENSTRUAL CYCLE AND HORMONAL CONTRACEPTIVES

The menstrual cycle is an essential part of the female reproductive life cycle. It is governed by the optimal interplay between hypothalamic, hypophyseal and ovarian hormones, and thus requires carefully coordinated and proper functioning of the hypothalamic-pituitary-ovarian (HPO) -axis. (Constantini et al. 2005; Sam & Frohman 2008; Davis & Hackney 2017, 2.) Multiple effects of fluctuating hormone levels include structural and functional changes in not only the female reproductive tract, but also in many other tissues, such as adipose tissue and brain (Constantini et al. 2005).

Several forms of hormonal contraceptives are available for a variety of purposes, such as birth control, menstrual manipulation, and the treatment of amenorrhea or painful menstrual symptoms (Lebrun et al. 2003; Shulman 2011; Martin et al. 2018). By inhibiting HPO-axis, hormonal contraceptives systematically control concentrations of endogenous sex hormones (Davis & Hackney 2017, 8). Different chemical formulations vary depending on the preparation, and therefore may have divergent effects on body systems. Previous studies have reported that hormonal contraceptives may alter, for instance, lipid profile, skin and mood. (Burrows & Peters 2007; Sabatini et al. 2011; Brynhildsen 2014). However, these studies cannot be considered conclusive due to the varying concentrations of exogenous hormones used in studies.

2.1 An overview of the hypothalamic-pituitary-ovarian axis

The HPO-axis consists of the hypothalamus, the pituitary and the ovaries, which constantly interact by sending chemical signals back and forth between them through cyclic production of gonadotropic and steroid hormones (Mikhael et al. 2019), exerting either positive or negative feedback effect at various levels of the HPO axis depending on the cycle phase (Messinis et al. 2014). These hormones include gonadotropin-releasing hormone (GnRH), luteinizing hormone (LH) and follicle-stimulating hormone (FSH), estrogen and progesterone (Ferin 2000; Kong et al. 2014; Mikhael et al. 2019.) Figure 1 represents the major components of this control system (Kong et al. 2014).
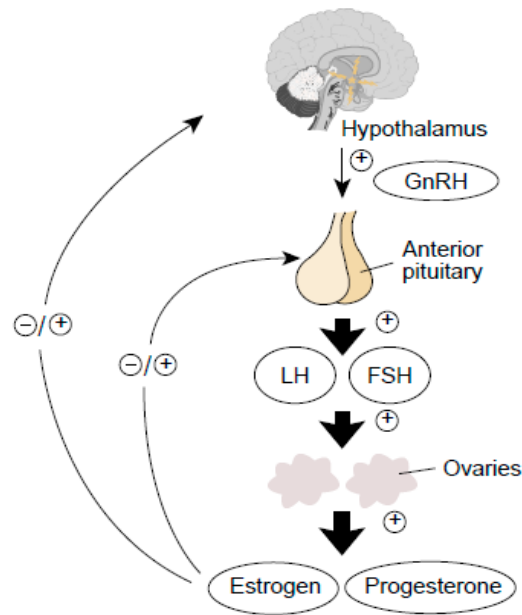
FIGURE 1. Representation of the HPO axis that forms the female hormonal system. (Kong et al. 2014)

2.1.1 Key regulatory hormones

GnRH is a tropic peptide hormone secreted from the hypothalamus by GnRH-expressing neurons in a pulsatile manner. This hormone has a stimulatory effect on the anterior pituitary, which induces the production of small glycoprotein hormones, LH and FSH (Marques et al. 2018.) The main responsibility of LH and FSH is to stimulate estrogen and progesterone production in the ovaries. Alongside their synchronized actions, they also have individual functions critical to ovarian changes during the normal menstrual cycle. LH is the predominant trigger for ovulation and contributes to the development and secretory function of corpus luteum. FSH, in turn, is pivotal for follicle maturation before ovulation. (De Jonge et al. 2001; Raju et al. 2013; Cahoreau et al. 2015; Orlowski & Sarao 2018; Guyton & Hall 2011, 988.)

Estrogen is a general term for a group of steroid hormones produced primarily by the ovaries, and to a lesser extent, in the adrenal gland and locally in other target tissues such as the adipose tissue (Wierman 2007; Guyton & Hall 2011, 991). The group consists of three main types of estrogen, each of which having crucial functions in the regulation of HPO-axis, and in various tissues, such as skin, bones, soft tissue and skeletal muscle. Estradiol-17β (estradiol) is responsible for primary and secondary female sex characteristics, and therefore is considered the most important estrogen in pre-menopausal women (Wierman 2007; Guyton & Hall 2011, 905, 993.) Estrone comes into play to complete the steep decline in the production of estradiol

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production after the onset of menopause, whereas placental estriol is proposed to affect fetal health during pregnancy (Keren et al. 1995, Kashork et al. 2002).

Estrogens have well-defined effects on metabolism and body composition. A decent amount of research confirms that the menopausal decline in estradiol is associated with fat accumulation with distribution shifting from subcutaneous to visceral compartments, impaired glucose metabolism and increased inflammatory markers (Faulds et al. 2012, Van Pelt et al. 2016). Estrogens exert their physiological effects by binding to the classical estrogen receptors, estrogen receptor alpha (ERα) and beta (ERβ), which are involved in the regulation of several significant physiological processes in humans (Jia et al. 2015).

Progesterone is a steroid hormone produced by the ovaries, placenta and adrenal gland. Besides the reproductive system, it also has extensive effects on the central nervous system, bones and the cardiovascular function. (Perrot-Aplanat et al. 1995; Graham et al. 1997; Genazzani et al. 2000; Taraborrelli 2015.) The main source of progesterone during the luteal phase is a temporary endocrine structure called the corpus luteum, which is composed of lutein cells. The purpose of this LH-dependent process is to prepare the endometrium for development of an embryo, as progesterone has some direct and indirect regulatory functions on specific ovarian molecules known to be involved in implantation of the fertilized egg. (Young & Lessey 2010; Barbieri 2014; Guyton & Hall 2011, 994.)

The feedback loop represented in the Figure 1 illustrates the precise coordination between ovarian hormones, the hypothalamus, and the pituitary gland (Kong et al. 2014). Estrogen and progesterone have synergistic inhibitory effects on LH and FSH production in the pituitary gland. In addition, the effects of estrogen extend to the hypothalamus, where it reduces GnRH secretion by altering the frequency of GnRH pulses. The hormone inhibin, which is released from the corpus luteum along with sex steroid hormones, inhibits FSH and LH as well. However, estrogen also has a positive feedback effect before ovulation when it significantly increases LH secretion. The reasons explaining this positive feedback effect of estrogen at mid-cycle are not completely understood. (Guyton & Hall 2011, 997.)

2.1.2 Ovaries

The ovaries, located on both sides of the uterus, are constantly undergoing structural and functional modifications. They have two main physiological responsibilities: 1) the production of estrogen and progesterone, and 2) the production and release of female gametes, termed oocytes. The major components of the ovary are the outer cortex, the inner medulla and the rete ovarii, called the hilum. (Smith 1940, Speroff & Fritz 2005, 107, Holesh & Lord 2019.) The biosynthesis of sex steroid hormones and the maturation of the follicles occur in the outer cortex, which is therefore considered a functional component of the ovaries (Speroff & Fritz 2005, 107, Wagner et al. 2020).

The formation of oocytes, called oogenesis, begins in fetal life. During oogenesis, fetal germ cells differentiate into primordial follicles that are required to undergo two more cell divisions to be called primary oocytes (Guyton & Hall 2011, 987). After the birth, the number of these primary oocytes gradually decline throughout the reproductive years of female life. Between the onset of puberty and menopause, 400 to 500 mature oocytes are expelled monthly from the ovaries and passed into the uterus via abdominal cavity. A single ovum develops into a fetus if the ovum is fertilized and implanted in the uterus. (Guyton & Hall 2011, 987; Holesh & Lord 2019; Wagner et al. 2020).

2.2 The hormonal regulation of the menstrual cycle

Typical length of a normal "eumenorrheic" menstrual cycle is generally 26–35 days, with median duration being 28 days (Dawson & Reilly 2008; Reed & Carr 2018). Due to individual times required for a follicle to mature completely, there is quite wide range of variation in the length of menstrual cycle (Thiyagarajan et al. 2019). The menstrual cycle is divided roughly into two halves, the follicular phase and the luteal phase, split by ovulation at the halfway. (Hackney 2017, 4; Dawson & Reilly 2008). As pointed out in Figure 2, the sequential function of these phases, driven by pituitary gonadotropins and ovarian hormones, is required to initiate a series of changes in the uterine endometrium and the ovaries.

Pituitary cycle

FSH LH

Ovarian cycle

Maturation of follicle
Ovulation
Corpus luteum

E2

P

Endometrial cycle

M

−12 −8 −4 0 +4 +8 +12

Follicular phase Luteal phase

Ovulatory phase
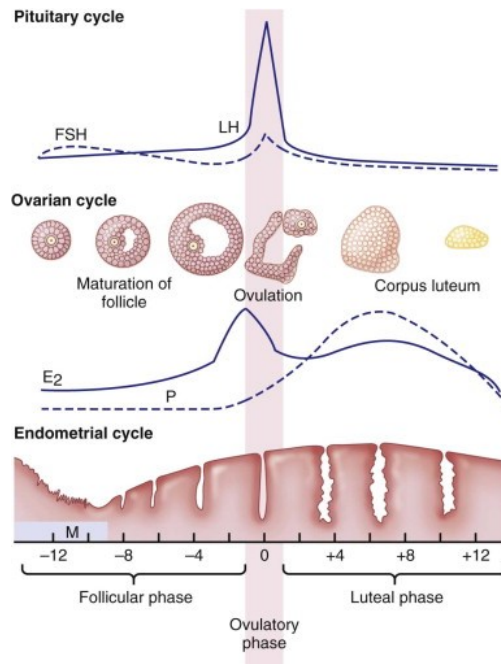
FIGURE 2. Changes in pituitary hormones, ovarian status and uterine endometrium across the menstrual cycle (Rebar & Erickson 2012, 1534). E2 = Estradiol, P = Progesterone

The period between the first day of menstruation and ovulation is called the follicular phase. It can be further distinguished into the FSH-dominant early follicular phase, and the late stages controlled primarily by LH. (Ziegler 2007.) The follicular phase starts with the menstruation, which is defined as bloody discharge of mucosal tissue from the inner lining of the uterus, characterized by low estradiol due to regression of corpus luteum from the previous cycle. The purpose of elevated FSH, in turn, is to increase proliferation of the granulosa cells and simultaneously upregulate the expression of LH receptors. Under the influence of FSH, the secretion rate of estradiol in the granulosa cells increases towards the second half of the follicular phase, which reinforces the stimulatory actions of GnRH on the LH production and proliferation of endometrial tissue. Eventually, this cascade of events results in a selection of dominant follicle while other follicles rupture away due to the degradative effects of slightly elevating progesterone. (Davis & Hackney 2017, 6; Vigil et al. 2017; Guyton & Hall 2011, 989.)

Ovulation is defined as the release of an ovum from the dominant follicle in response to sharp spike of LH, which occurs approximately at mid cycle. According to Guyton & Hall (2011, 990), suggested mechanism of ovulation consists of following consecutive steps. First, substantially elevated LH and FSH have synergistic effects on the follicle, which swells rapidly. Simultaneously LH converts the granulosa and theca cells to progesterone-secreting cells, while

estrogen production decreases drastically. Second, the follicle continues to swell due to rapid angiogenesis, prostaglandin-induced vasodilation and the release of proteolytic enzymes weakening the follicle wall. Finally, the follicle ruptures, and the ovum is expelled to the uterus. (Dawson & Reilly 2008; Guyton & Hall 2011, 990; Reed & Carr 2018.)

After ovulation, the remaining granulosa and theca cells comprise the corpus luteum, which gives the name "luteal phase" for the final period of the menstrual cycle. Although the corpus luteum is the source of both estradiol and progesterone, the latter plays a dominant role due to greater secretion rate. If the ovum is not fertilized, loss of secretory properties of the corpus luteum lead to dramatic decline in both estradiol and progesterone. Final degradation of the corpus luteum occurs when hormone inhibin greatly prevents FSH and LH secretion. Consequently, low levels of ovarian hormones together with decreased inhibin remove the feedback inhibition of the anterior pituitary gland, allowing onset of the new cycle. (Brannian & Stouffer 1991; Davis & Hackney 2017, 7; Guyton & Hall 2011, 991.)

2.3 Hormonal contraceptives

Hormonal contraceptive refers to any exogenous hormone that changes endogenous endocrine function and prevents pregnancy (Rivera et al. 1999). Several options, such as oral pills, intrauterine devices, injections, transdermal patches, implants and vaginal rings are available (Martin & Elliot-Sale 2016). About 22% of the general population uses oral contraceptives and 9 % other forms of hormonal contraceptives (Cea-Soriano et al. 2014). Approximately half of female athletes use oral contraceptives (Brynhildsen et al. 1997; Torstveit & Sundgot-Borgen 2005) but the prevalence data of other methods is lacking (Martin & Elliot-Sale 2016). The main purpose of hormonal contraception is prevention of unwanted pregnancy, but they are frequently used also for cycle regulation, the treatment of painful menstruation or to protect bone density in amenorrheic athletes (Rickenlund et al. 2004). Because estrogen has important role in maintaining bone mass, oral contraceptives may prevent bone loss in premenopausal women (Scholes et al. 2010). Furthermore, some studies suggest that hormonal contraceptives have anti-inflammatory effects, as they may as they may increase neutrophils and cortisol compared to non-users of the oral contraceptives or men (Meulenberg & Hofman 1990; Timmons et al. 2005).

Brain
CNS
Hypothalamus
Pituitary ← OCP inhibits FSH and LH release
FSH | LH
Ovary
Estrogen | Progestogen
Uterus

Dormant follicle development

Exogenous supply of estrogen and progestogen as per OCP formulation
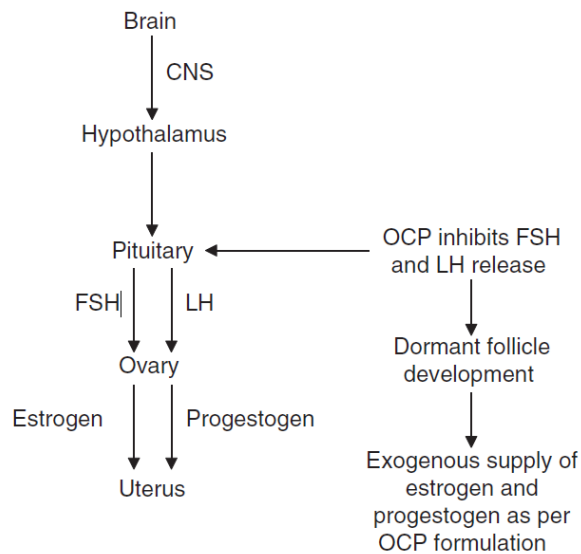
FIGURE 3. Basic mechanism of hormonal contraceptives (Burrows & Peters 2007). OCP = The oral contraceptive pill.

The primary mechanism of action of all combined preparations is the prevention of ovulation (Figure 3) (Burrows & Peters 2007). Synthetically administered estrogen exerts its anti-ovulatory effects via preventing an FSH surge, which suppresses follicular maturation and subsequent release of oocyte. Progestin, on the other hand, prevents pregnancy by two independent mechanisms. First, it acts as an inhibitory brake to ovulation by blocking the LH surge. Second, it thickens cervical mucus and has antiproliferative effects, making the endometrium hostile to sperm migration and embryo implantation. (Baird & van r 1993; Dhont 2010.)

Hormonal contraceptive formulations fall into two main categories based on the type: 1) combined methods that contain both synthetic estrogen and progesterone, and 2) progestogen-only methods that contain only progesterone (Davis & Hackney 2017, 8–10). Combined methods usually contain Ethinyl Estradiol (EE) and progestin in doses equivalent to the follicular phase (Dawson & Reilly 2008). They can be further divided into monophasic and phasic preparations, depending on the concentration of hormones provided by the pill (Figure 4). Phasic approach is developed to mimic the natural menstrual cycle and thus minimize the incidence of undesirable side effects of oral contraceptives (Davis & Hackney 2017, 9; Hale 1987), although the extent to which the phasic pills prevent for instance disturbed bleeding patterns is debated (Van Vliet et al. 2011).

Generally, combined oral contraceptives are administered periodically with a hormone-free interval in between the cycles (Figure 4). During the active phase, the pill is ingested daily from day one to 21. After the active phase, either placebo pill or no pill is taken, which is termed as the inactive phase. In the absence of exogenous hormones, endogenous estrogen gradually rises while progesterone stays suppressed, which results in light menstruation called withdrawal bleeding. In monophasic preparations, the dosage of EE ranges between 0.02 and 0.05 mg, whereas phasic preparations may have either constant or varying concentration of EE. Concentration and type of progestogen fluctuates considerably in both monophasic and phasic preparations depending on the brand. (Rechichi 2008.) Progestogen-only pills are taken daily without withdrawal phase. However, they are considered less effective compared to combined methods due to inconsistency in ovulation inhibition observed in some studies. (Davis & Hackney 2017, 10.)
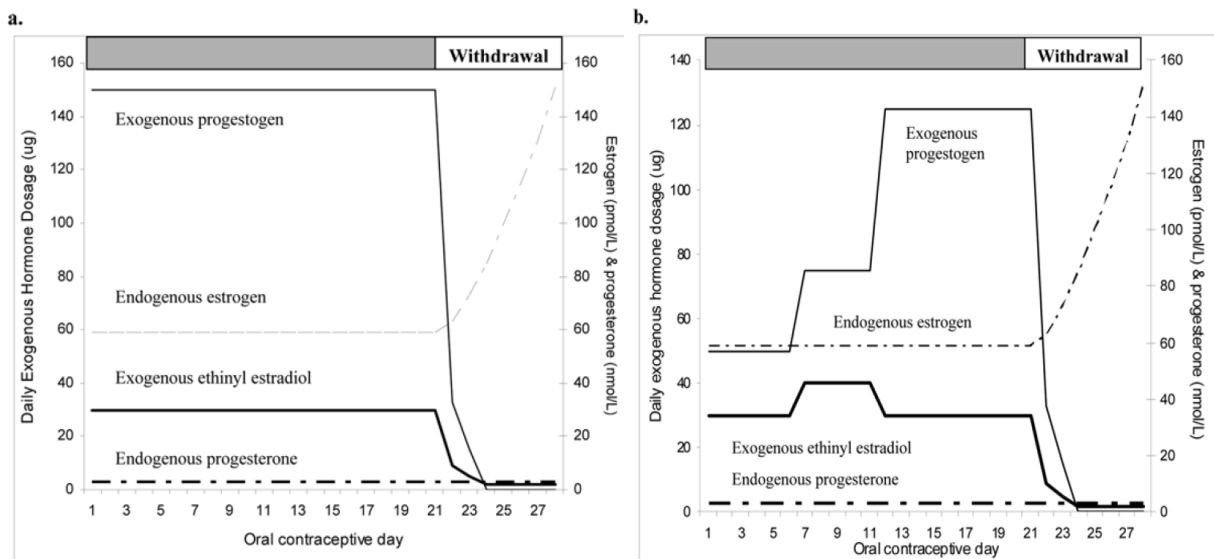
FIGURE 4. 28-day oral contraceptive cycle with variations of endogenous and exogenous hormones and withdrawal phases for a) monophasic and b) triphasic preparations. (Rechichi et al. 2009).

3   REGULATION OF FOOD INTAKE

In recent years, physiological systems controlling energy homeostasis and food intake have been under the extensive investigation. Signals released from adipose tissue, the pancreas and gastrointestinal tract are inevitably linked to food intake modulating central circuits in the brain. (Stanley et al. 2005.) Figure 5 represents the complex net of signals regulating energy homeostasis. Two hormones of this regulation net, the anorexigenic hormone leptin and the orexigenic hormone ghrelin, are recognized to act as primary regulators of energy balance, defined as stable bodyweight resulting from equality between energy intake and energy expenditure (Sahu 2003; Klok et al. 2007; Hill et al. 2013.) Anorexigenic hormones, such as leptin and insulin, produce a negative energy balance by suppressing the drive to eat, whereas orexigenic hormone ghrelin leads to appetite stimulation (Stanley et al. 2005). When leptin, insulin or ghrelin receptors are activated, different signaling cascades lead to these changes in food intake (Sahu 2003; Simpson et al. 2009; Loh et al. 2017).

FIGURE 5. Regulation of energy homeostasis by gastrointestinal hormones and adiposity signals that exert a negative (-) or positive (+) effect on energy balance via hypothalamic and brainstem neuronal circuits (Stanley et al. 2005).

3.1 Leptin

The product of obesity (ob) gene, leptin, has attracted interest of researchers for decades. In 1950, Ingalls et al. found that the genetic defect in mice resulted in severe hyperphagia and obesity. Later, Zhang et al. (1994) identified the mouse ob gene and found its human counterpart on chromosome 7. They demonstrated that the ob 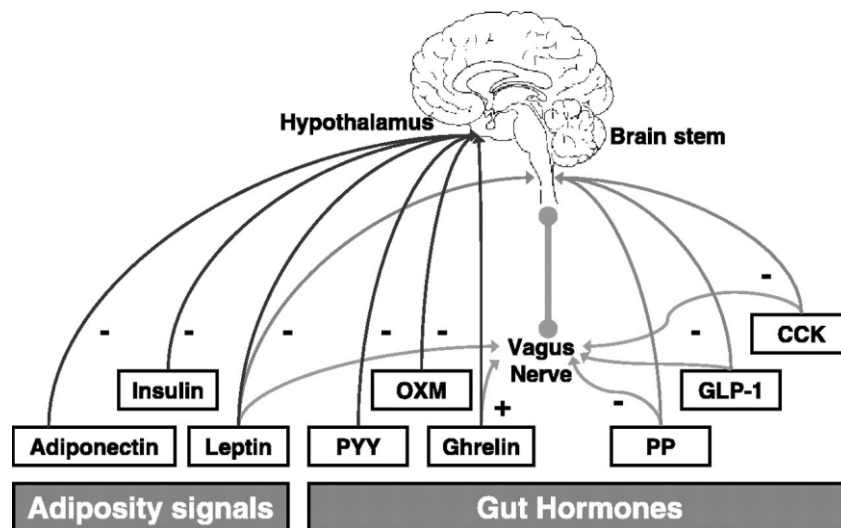gene encoded a specific protein containing 167 amino acid, which was named leptin, and that it has a potential regulatory role in obesity. (Zhang et al. 1994.) To date, it has been established that the ob gene is highly expressed in white and brown adipose tissue, and to a lesser extent, in the placenta, heart, gastric epithelium, and possibly the brain (Green et al. 1995; Pelleymounter et al. 1995; Bado et al. 1998; Lönnqvist et al. 1999; Ahima et al. 2000).

Leptin has been considered to play a pivotal role in long-term energy balance because it circulates in the blood in proportion to body fat (Considine et al. 1996; Chin-Chance et al. 2000; Klok et al. 2007; Myers et al. 2010). Increased fat mass results in elevated leptin levels, which leads to the suppression of appetite until weight is lost. In addition, leptin has been shown to accelerate energy expenditure in an overfed state. Conversely, decreased fat mass results in a decrease of leptin, which stimulates appetite, suppresses energy expenditure, and modulates both neuroendocrine and immune function. These functions are needed to conserve energy stores through the restoration of lost fat mass. (Bado et al. 1998; Ahima et al. 2000; Kahn et al. 2005; Friedman 2016.) However, an increasing number of studies indicate that no significant change in fat mass is required to cause fluctuations in leptin levels. Instead, leptin may also respond to short-term energy imbalances. (Kolaczynski et al. 1996; Chin-Chance et al. 2000; Blüher & Mantzoros 2009.)

3.1.1 Leptin actions in the brain

Leptin has access to the brain through the blood-brain barrier, where its main purpose is to initiate actions that contribute to maintenance of energy stores at a relatively stable level. After binding to its receptor (LEP-R), which is highly expressed in the hypothalamic region, leptin inhibits food intake while stimulating energy expenditure. (Matson et al. 1997; Bado et al. 1998; Elmquist et al. 1999, Klok et al. 2007; Myers et al. 2010; Hussain & Khan 2017.) The study of Mistry et al (1997) confirmed the important role of hypothalamus in the central actions of leptin. They found that that administration of leptin to the area near the hypothalamus significantly reduced food intake in mice. Deficiency of either leptin or LEP-R, in turn, induces physiological

response to starvation, which leads to hyperphagia and weight gain (Morris & Rui 2009; Myers et al. 2010).

Studies conducted in humans support the results obtained in mice. Larsson et al. (1998) found that leptin levels were negatively correlated with total energy intake in postmenopausal women. A case study of Farooqi et al. (2007) evaluated the association between exogenous leptin administration and eating behavior in subjects with leptin deficiency. They ascertained that leptin treatment significantly reduced energy intake and hunger ratings while increasing postprandial satiety, which establishes a link between leptin and the brain neuronal circuits responsible for perception of food reward and satiety (Farooqi et al. 2007).

Previous studies do not provide any conclusive evidence for the mechanism underlying the regulatory role of leptin in energy expenditure. It has been hypothesized that leptin enhances energy metabolism and sympathetic activation via increased neuroelectric activity when it binds to LEP-R on the proopiomelanocortin (POMC) neurons located in the arcuate nucleus (ARC). (Marsh et al. 1999.) Furthermore, leptin drives the activity of major signaling pathways, such as the Janus kinase (JAK) -signal transducers and activators of transcription (STAT) intracellular signaling pathway, which are involved in multiple regulatory functions in the body, including energy homeostasis. (Su et al. 2012; Ladyman & Grattan 2013; Park & Ahima 2014.)

3.1.2   Leptin and obesity

Given the high expression of the ob genes in adipose tissue, it is conceivable that there is an association between leptin and both body mass index (BMI) and body fat. As previously stated, a vast array of literature confirms that serum leptin levels are higher in the obese subjects compared to normal weight subjects. (Boden et al. 1996; Considine et al. 1996; Hickey et al. 1996; Rosenbaum et al. 1996; Couillard et al. 1997; Al-Harithy et al. 2006; Monti et al. 2006; Myers et al. 2010; Rafique et al. 2018).

Interestingly, high leptin levels in obese individuals are in contradiction with well-investigated appetite-inhibiting effects of leptin. This discrepancy has led to the term "leptin resistance" that often coexists with insulin resistance and other metabolic dysfunctions (Myers et al. 2010; Gruzdeva et al. 2019). In fact, it has been proposed that leptin and insulin resistance can be explained by similar cellular mechanisms (Myers et al. 2010). Although the pathogenesis has not been fully elucidated, the two main hypotheses have received the most attention to date: 1) leptin resistance results from impaired leptin transport to sites of action through the blood-brain-

barrier (Banks 2012; Kastin et al. 1999), and 2) disruption of leptin signaling pathways interferes with leptin's access to its target neurons (El-Haschimi et al. 2000). Moreover, it has been suggested that obesity-related chronic low-grade inflammation, endoplasmic reticulum stress, and defective autophagy may contribute to leptin resistance (Zhang et al. 2008; Ozcan et al. 2009; Myers et al. 2010).

3.1.3 Leptin and glucose metabolism

It is generally agreed that leptin and glucose metabolism are intricately linked. Leptin directly controls insulin secretion by binding on LEP-R in pancreatic β-cells, and centrally by suppressing insulin signaling pathways in the liver and other insulin-sensitive tissues. (Denroche et al. 2012.) Insulin, that shares similar effects on food intake and energy metabolism with leptin, stimulates leptin synthesis and secretion (Kamohara et al. 1997; Seufert et al. 1999). This dual hormonal feedback loop, termed the adipoinsular axis, significantly governs metabolic responses to feeding (Kieffer & Habener 2000).

There is some evidence that exogenously administered leptin lowers blood glucose levels in mice (Schwartz et al. 1996, Levin et al. 1996). The effect was seen in some studies independently of body weight, energy intake and insulin (Seufert et al. 1999, Lam et al. 2004; Ueno et al. 2006; Kojima et al. 2009), which has provided impetus for the development of novel leptin-based treatments for the early metabolic derangements (Ueno et al. 2006). In humans with congenital leptin deficiency or lipodystrophy, leptin treatment has yielded promising results in hyperinsulinemia among other metabolic abnormalities in few studies (Petersen et al. 2002; Oral et al. 2002; Gibson et al. 2004; Licinio et al. 2004). However, a similar systematic effect on glucose metabolism has not been demonstrated in healthy individuals.

3.1.4 Leptin and other satiety signals

Because leptin is an integral part of complicated system of energy balance regulation, it has interactions with other satiety signals as well. Matson et al. (1997) found that leptin may have synergistic effects with gastrointestinal peptide hormone, CCK, that stimulates the digestion of fat and protein acting as a hunger suppressant (Hirschberg 2012). After intraperitoneal administration of leptin and CCK in mice total daily caloric intake was significantly reduced compared to leptin alone (Matson et al. 1997). Other researchers have confirmed this feedback loop between CCK and leptin in rats (Guilmeau et al. 2003), but it has not been examined in healthy humans.

3.2 Ghrelin

Ghrelin is a novel peptide hormone that has opposite effects to leptin. It is the only known hormone that powerfully increases food intake in humans (Wren et al. 2001; Cummings et al. 2005; Cummings & Overduin 2007). Ghrelin is produced primarily by the stomach gastric cells, with a small fraction secreted by the hypothalamus, the small intestine and the pancreas, which respond rapidly to fluctuations in energy status by increasing ghrelin secretion during fasting and decreasing it shortly after eating (Cummings et al. 2001; Tschöp et al. 2001). The tendency of ghrelin to surge prior to meals has raised the suggestion of its potential role in meal initiation (Cummings & Overduin 2007). Over a long term, ghrelin promotes weight gain and adiposity by the modulation of lipid metabolism and the increase of appetite (Theander-Carrillo et al. 2006). Against this background, ghrelin has been referred as a key regulator of energy balance (Pradhan et al. 2014).

The molecular mechanisms regulating secretion of ghrelin are not yet completely understood, however, its release is part of network of modulatory signals, mediated by G-protein coupled receptors (GPRCs) (Engelstoft et al. 2013). GPRCs refer to a large group of cell surface receptors that have a plethora of essential signaling functions, including the cell responses to external stimulants such as nutrients (Rosenbaum et al. 2009). When ghrelin binds to the specific neurons in the hypothalamic nuclei, neuronal projections to other appetite regulating centers are initiated (Howick et al. 2016). Ghrelin reaches the hypothalamic food intake regulatory centers after passing the blood-brain barrier (Banks et al. 2002) or via vagal afferents and neurons (Date et al. 2002). Furthermore, it has been shown that ghrelin is involved in several significant peripheral and central physiological functions such as glucose metabolism, insulin secretion, immune function, water balance, gastric emptying and gastric acid secretion, memory, anxiety, sleep, energy expenditure, reproductive function and cardiovascular function (Figure 6) (Sakata & Sakai 2010; Al Massadi et al. 2011).
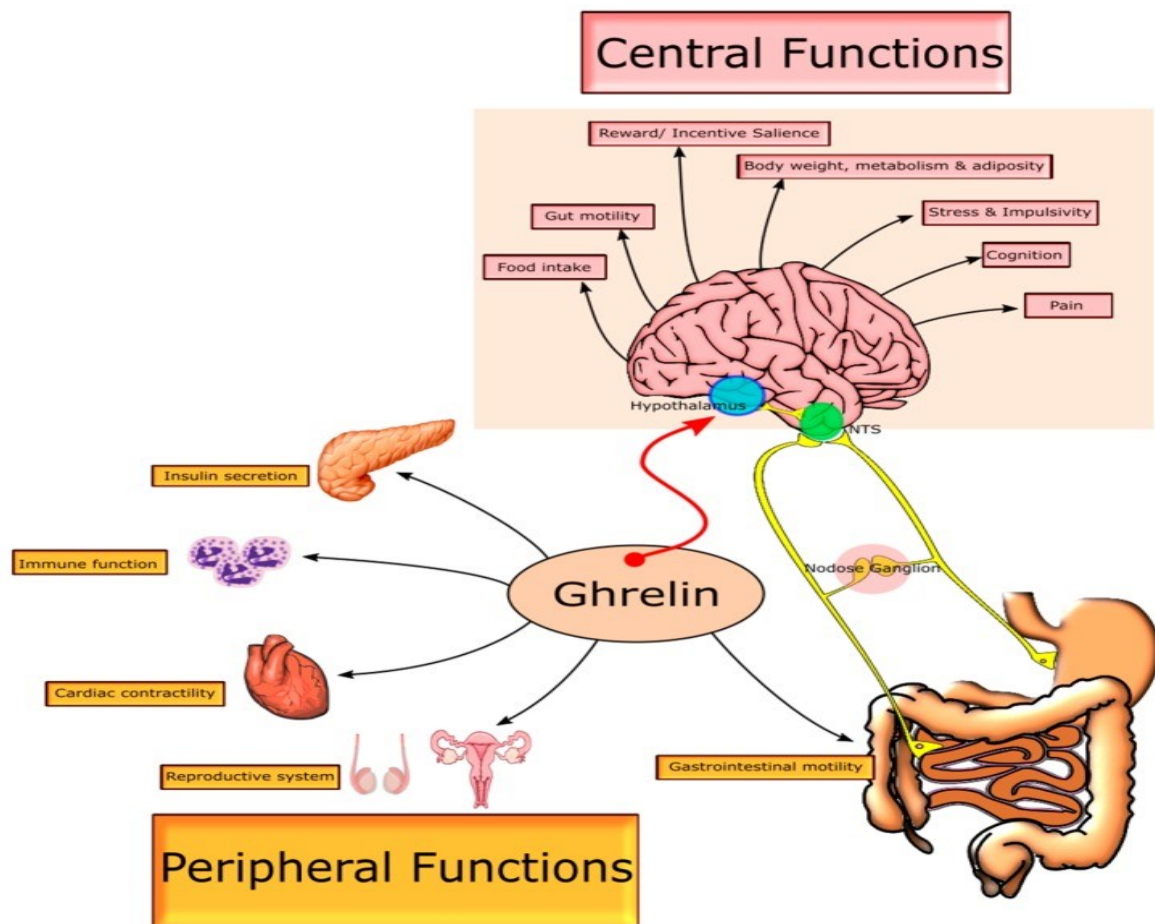
FIGURE 6. Documented actions of ghrelin after exogenous administration or endogenous release from the stomach. Ghrelin crosses the blood-brain barrier (red arrow) and activates GHSR-1 in the ARC or transfers to the CNS via vagal afferents, leading to several peripherally or centrally mediated functions. (Howick et al. 2016.)

3.2.1 Ghrelin and energy balance

From the evolutionary point of view, purpose of ghrelin may have been to ensure survival by inducing behavioral and physiological changes during times when food was not available. In low energy balance, increased ghrelin drives food-seeking behavior and influences on substrates involved in the mesolimbic system, reinforcing the food reward. (Skibicka & Dickson 2011; Perello & Dickson 2015; Zigman et al. 2016; Al Massadi et al. 2019). Correspondingly, in positive energy balance ghrelin levels decrease. Several studies have confirmed that ghrelin levels are lower in obese individuals compared to those in negative energy balance. (Tschöp et al. 2000; Otto et al. 2001.)

Suppressed release of ghrelin in obese individuals is associated with several factors. The commonly observed obesity-related insulin resistance and hyperleptinemia contribute to low levels of ghrelin because insulin inhibits ghrelin secretion (Maier et al. 2008; Koliaki et al. 2010). In addition, it has been suggested that hyperleptinemia and elevated cytokines typical of obesity may inhibit the release of ghrelin (Shintani et al. 2001). Reduced ghrelin levels of obese individuals have shown to return normal after weight loss, from about 340 – 450 pg/mL to 450 – 600 pg/mL, with a reference range of 520 to 700 pg/mL in normal weight subjects (Mayo Clinic Laboratories, s.a.). Similarly, it has been demonstrated that weight gain and refeeding normalize high ghrelin levels in subjects suffering from anorexia nervosa (Otto et al. 2001; Soriano-Guillén et al. 2004; Schalla & Stengel 2018).

Besides reduced fasting levels, it has been suggested that obese subjects have abnormal post-prandial ghrelin responses. While the ghrelin levels peak preprandially and decrease after eating in normal weight subjects, in obese subjects this response appears to be blunted. (English et al. 2002, Koliaki et al. 2010.) As a result, dysregulation of satiety pathways may lead to continued food intake and eventually, further weight gain (English et al. 2002; Maier et al. 2008; Koliaki et al. 2010; Zigman et al. 2016). In addition, ghrelin promotes adiposity directly, and independently of its orexigenic actions, by increasing the expression of specific fat storage-inducing proteins, reducing lipid mobilization and stimulating the lipogenesis in the liver (Theander-Carrillo et al. 2006; Davies et al. 2009; Lv et al. 2018).

3.2.2 Forms of ghrelin

Ghrelin circulates in two major forms, acylated and unacylated form. These both forms of ghrelin are recognized to be involved in energy balance regulation, but only acylated ghrelin (AG) has been shown to stimulate appetite when administered exogenously. (Mackelvie et al. 2007.) Most of the human ghrelin studies have assessed total ghrelin, that consists of both AG and UnAG ghrelin. However, total ghrelin reflects primarily the amount of UnAG, because the AG represents only about 10% of total plasma ghrelin (Spiegel et al. 2011; Cappellari & Barazzoni 2018).

Ghrelin acylation is a post-translational process in which the hydroxyl group of the specific amino acid is acylated with a fatty acid that allows ghrelin peptide to bind and activate the classical ghrelin receptor, the growth hormone secretagogue receptor (GHSR)-1a (Al Massadi et al. 2011; Cappellari & Barazzoni 2018). Most of the physiological actions of ghrelin are likely mediated by AG binding the GHSR-1a, localized in the hypothalamus and peripherally

in several tissues, such as heart and adipose tissue (Papotti et al. 2000; Al Massadi et al. 2011; Cappellari & Barazzoni 2018). When AG binds to GHSR-1a, it mediates numerous effects including the stimulation of food intake and growth hormone release from the pituitary gland (Kojima et al. 1999).

The precise physiological significance of UnAG has been a matter of debate. Earlier studies have failed to demonstrate that UnAG binds to GHSR-1a, thus it has been regarded as biologically inactive form of ghrelin (Al Massadi et al. 2001). Nevertheless, lately UnAG has made its way into the field of ghrelin studies as it has been suggested that UnAG may regulate feeding independently from GHSR-1a (Toshinai et al. 2006; Delhanty et al. 2013). It may also be involved in skeletal muscle energy metabolism via insulin signaling, tissue inflammation, and redox activities (Cappellari & Barazzoni 2018). Delhanty et al. (2013) have confirmed that UnAG appears to have important metabolic actions related to inhibition of AG levels and improvement of postprandial glycaemia, which has inspired the suggestion that UnAG might be used for the development of new potential drugs for metabolic disorders (Delhanty et al. 2013).

It has been emphasized that UnAG and AG should be distinguished from each other, because they have different postprandial responses (Dardzínska et al. 2014). Dardzínska et al. (2014) found that among non-obese subjects, UnAG levels did not change while AG levels decreased in response to a standard meal. Oppositely, in obese subjects UnAG levels diminished and AG levels remained stable (Dardzínska et al 2014). In addition, Mizutani et al. (2009) reported that AG and UnAG are localized differently in the rat gastric mucosa, with UnAG in both gastric open and closed cells and AG only in closed cells. They also found that lower gastric pH enhanced UnAG secretion (Mizutani et al. 2009). Although this has not been studied in humans, overall, these findings provide reassurance regarding different physiological roles of these two forms of ghrelin (Cappellari & Barazzoni 2018).

3.2.3   Ghrelin and macronutrient distribution

Macronutrient distribution of ingested meal has influence on ghrelin. After a glucose tolerance test or carbohydrate-rich meals, ghrelin is suppressed most effectively (Shiiya et al. 2002; dit El Khoury et al. 2006; Monteleone et al. 2003). There are some speculations that significant rise of insulin after carbohydrate ingestion may have a role in suppression of ghrelin (Erdmann et al. 2003), given that the inverse relationship between them has been established in several studies (Möhlig et al. 2003; Saad et al. 2002; Flanagan et al. 2003). Furthermore, carbohydrates

are absorbed rapidly, which may partly account for the strong postprandial suppression of ghrelin (Koliaki et al. 2010).

In contrast, studies investigating the ghrelin response after protein- or fat-rich meals have not achieved a complete consensus. Blom et al. (2006) found that protein induced more effective ghrelin suppression compared to carbohydrates. This is supported by Al Awar et al. (2005) and dit El Khoury et al. (2006), who suggested more prolonged suppression of ghrelin after the protein meal compared to the meal containing more fat or carbohydrates. Curiously, Erdmann et al. (2003; 2004) observed an increase in ghrelin after high-protein meal. In the case of high-fat meals, results have been contradictory but generally indicate a reduction from baseline, albeit in a weak and delayed manner (Erdmann et al. 2003; Monteleone et al. 2003; Koliaki et al. 2010). Overall, these controversies may reflect differences between the experimental designs of studies (Koliaki et al. 2010), as well as the absence of the relationship between vagal neural mechanisms and post-prandial ghrelin secretion during the digestive processes (Erdmann et al. 2003).

3.3 Insulin and glucose

Insulin is a polypeptide hormone secreted from pancreatic β-cells in response to eating. In terms of energy balance regulation, insulin does not differ greatly from leptin: it correlates positively with body fat, increases during a positive energy balance, and decreases in a negative energy balance (Benoit et al. 2004; Plum et al. 2006). In addition, it may be involved in regulation of energy expenditure through thermogenic activity (Danforth 1983).

Peripheral actions of insulin are well known, but the central mechanisms behind its precise regulatory function are less understood (Loh et al. 2017). Insulin receptors (IRs) in the brain are located in hypothalamic nuclei, which are known to control appetite and energy homeostasis (Havrankova et al. 1978). In this region, neurons expressing the both IRs and LEP-Rs are classified into two neuronal populations based on their specific effect on appetite. Anorexigenic group consists of the pituitary precursor POMC and the neuropeptide cocaineamphetamine-regulated-transcript (CART), whereas orexigenic group includes neuropeptide Y (NPY) and agouti-related peptide (AgRP). These neurons release the melanocortins that have extensive effects on food intake and energy expenditure (Lau & Herzog 2014). Leptin and insulin activate the anorexigenic neurons and inhibit the orexigenic neurons, resulting in enhanced appetite control (Schwartz ym. 1991; Benoit et al. 2002).

Three factors are regulating glucose homeostasis to maintain levels in a narrow range between 4 and 7 nmol/L in healthy individuals: 1) glucose absorption from the intestine 2) glucose production by the liver, and 3) glucose uptake and metabolism by peripheral tissues (Saltiel & Kahn 2001). The role of insulin is to decrease glucose production by the liver and increase glucose uptake in muscle and fat tissue by stimulating the glucose transporter GLUT4 (Schwartsburd 2017). In addition, it has profound effects on anabolic and catabolic pathways of cellular metabolism: it stimulates lipogenesis, protein synthesis and glycogenesis, and inhibits degradation of stored energy. In insulin resistance or deficiency, these processes are dysregulated, which leads to elevation of fasting and postprandial glucose and lipid levels (Saltiel & Kahn 2001).

4 THE MENSTRUAL CYCLE AND FOOD INTAKE

Despite the methodological variations, a considerable amount of evidence supports the phenomenon of greater self-reported food intake during the luteal phase compared the follicular phase, mainly due to appetite stimulating or inhibiting effects of sex hormones (Gilbert & Gillman 1956; Bancroft et al 1988; Dye & Blundell 1997; Hirschberg et al. 2012). The effects of synthetically administered estradiol and progesterone on food intake are contradictory, as some studies have reported that hormonal contraceptive use increases food intake (Wallace et al. 1987; Eck et al. 1997) whereas others do not report any significant differences to non-users (Procter-Gray et al. 2008; McNeil et al. 1991).

4.1 Changes of food intake and cravings across the menstrual cycle

The link between eating behavior and the function of the hypothalamic-pituitary-gonadal axis in the female of numerous species is deeply rooted in evolution (Schneider 2006; Hirschberg 2012). It is well-documented that estradiol inhibits food intake whereas progesterone may have opposite effects (Hirschberg et al. 2012). For instance, rodents and primates eat less around the time of ovulation (Asarian & Geary 2006), which may reflect motivational aspects for preferring mate-seeking behavior over feeding (Schneider 2006). The similar cyclical variations have been observed in humans. Energy intake has been reported to be at its lowest during ovulation and highest in the luteal phase, reflecting the orexigenic effects of progesterone (Buffenstein et al. 1995). In the luteal phase, caloric intake has been shown to increase by 90-500 kcal compared to the follicular phase. (Martini et al. 1994; Barr et al. 1995; Buffenstein et al. 1995; Dye & Blundell 1997; Li et al. 1999; Pelkman et al. 2001; Cross et al. 2001; Bryant et al. 2006; Reed et al. 2008). In the long term, this relatively high increase in energy consumption during one-half of the menstrual cycle may have significant influence on energy balance and body weight.

It is reasonable to presume that increased energy intake is associated, at least partly, to the more frequently reported cravings for energy-dense foods during the luteal phase (Davidsen et al. 2007). A craving is defined as a powerful desire for a particular food, and it is experienced as more intensive and selective than usual hunger (Ronzio 2003, 190). In the context of the menstrual cycle, it has been suggested that food cravings might be driven by hormones (Ronzio 2003, 190; Davidsen et al. 2007).
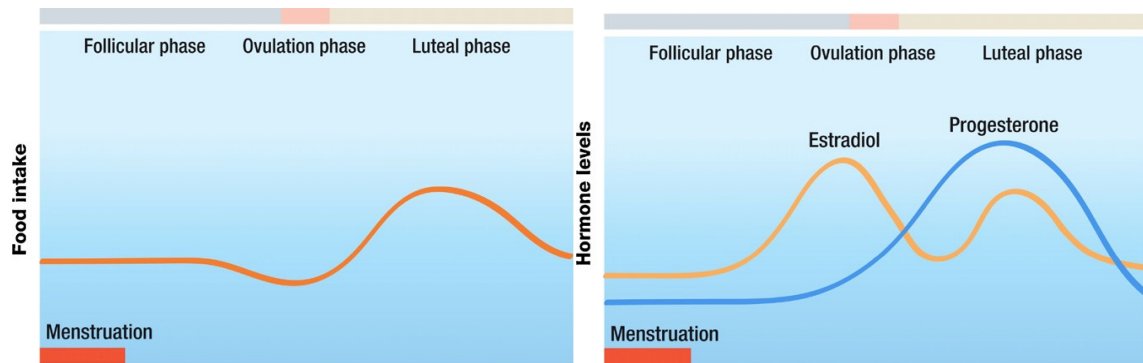
FIGURE 7. Changing food intake in relationship with estradiol and progesterone. Food intake decreases during the late follicular, high-estradiol phase before ovulation and elevates in the luteal phase when progesterone is high. (Hirschberg 2012.)

4.1.1　　　　The role of estradiol and progesterone

The mechanism underlying the anorexigenic effect of estradiol is related to multiple complex signaling pathways initiated with activation of estrogen receptors in the hypothalamus (Butera 2010; Eckel 2011). Estradiol inhibits NPY and AgRP neurons in the ARC (Olofsson et al. 2009) and stimulates anorexigenic activity by increasing the excitability of POMC neurons in rats (Smith et al. 2014). This is supported by the finding that the increased food intake in ovariectomized rats can be reversed by estrogen treatment (Butera et al. 2010). In addition, it has been shown that the satiety effect of CCK is potentiated by estradiol injection in rats (Lindén 1990; Asarian & Geary 2007; Geary 2007). The major drawback, however, is that these associations are difficult to study in humans. Evidence of estradiol as an appetite suppressant in humans is based on increased prevalence of obesity after the cessation of estrogen production in menopause (Lizcano & Guzmán 2014), and fluctuations in food intake during the menstrual cycle, respectively.

Appetite-regulating effects of progesterone are less understood than those of estradiol. There is no phase during the menstrual cycle when only progesterone is elevated, thus it is impossible to isolate progesterone from estradiol (Stachenfeld & Taylor 2014; Townsend 2016). Furthermore, following speculations are mainly derived from studies observing mice, thus results cannot be directly extrapolated to humans. Only pharmacological doses of progesterone have been shown to influence food intake in rats (Wade 1978), whereas progestin-only contraceptive drug did not exert any effect on eating in healthy women (Pelkman et al. 2001). It has been suggested that progesterone may antagonize some of the metabolic actions of estradiol, which arises the puzzling question of progesterone's potential to reverse the

anorexigenic effect of estradiol (Frankowich & Lebrun 2000; Townsend 2016). Likewise, Krishnan et al. (2016) speculated that progesterone may diminish the impact of estradiol in the luteal phase, leading to increased food intake. In contrast with these speculations, in their review Czaja et al. (1978) failed to provide adequate proof that progesterone antagonizes the anorexigenic effect of estradiol in primates or rats. The findings of Yu et al. (2011) are similar: the effect of estradiol was not attenuated with co-administrated progesterone, which highlights the role of estradiol as a primary regulator of food intake in rats (Yu et el. 2011). Regardless of inconsistencies in previous studies, it cannot be excluded that progesterone may possess some sort of orexigenic activity given the repeatedly reported increased energy intake and cravings during the progesterone-dominated luteal phase in both human and animal studies (Rosenblatt et al. 1980; Dye & Blundell 1997; Hirschberg 2012; Krishnan et al. 2016).

One possible suggestion that contributes to higher energy intake is that the energy expenditure may be increased during the luteal phase, although the magnitude of increment varies between studies (Davidsen et al. 2007). The luteal phase increase in 24-h energy expenditure has been shown to range between 89–279 kcal (Webb 1986; Bisdee et al. 1898). It has been proposed that increase in energy expenditure in the luteal phase may result at least partly from actions of progesterone-mediated metabolic effects (Howe et al. 1993). For instance, progesterone may activate the thermogenic activity (Barton & Wiesner 1945; Rothchild & Rapport 1952), which is supported by higher basal body temperatures after progesterone administration (Israel & Schneller 1950) as well as during the latter half of menstrual cycle (Marshall 1963; Baker & Driver 2007).

4.1.2 Menstrual cycle, cravings, and macronutrient distribution

The menstrual cycle-related cravings, often experienced in the luteal phase, have been linked to premenstrual syndrome (PMS) (Davidsen et al 2007), defined as cyclically appearing cluster of emotional and physical symptoms from mood swings to fatigue (Dickerson et al. 2003). It has been suggested that the association between PMS and cravings might be explained by their partially unknown common biochemical basis, including the multifactorial combination of genetics, neurotransmitters, and sex steroid hormones (Dickerson et al. 2003; Davidsen et al. 2007). Indeed, it has been reported that women suffering from PMS may experience more intense luteal phase-cravings compared to women without PMS (Both-Orthman et al. 1988), possibly due to higher sensitivity to neuroendocrinological changes (Bancroft et al. 1991).

A general increase in appetite during the luteal phase is in line with frequently reported cravings for foods with high content of energy, fat, and carbohydrate (Davidsen et al. 2007; Gorczyga et al. 2016). In attempt to elucidate these preferences, it has been proposed that the perception of sweetness across the menstrual cycle may be altered. (Davidsen et al. 2007.) Some studies have reported that sweet tastes and smells are increased in the luteal phase (Bowen & Grunberg 1990; Venditti 2020), which could explain why highly palatable foods, such as chocolate, are typical objects of cravings in women (Rozin et al. 1991). Nevertheless, the specific mechanism leading to higher prevalence of pre-menstrual cravings is challenging to discover due to the variety of biological, psychological, and cultural factors that contribute to food intake.

In accordance with increased cravings and energy intake, there is some evidence that women consume more foods rich in carbohydrates and fat during the luteal phase (Martini et al. 1994; Li et al. 1999; Bryant et al. 2006). In contrast, some studies have observed increased intake of protein, and specifically animal protein, during the luteal phase (Gorczyga et al. 2016), while some studies do not report any change in food preference between phases (Dye & Blundell 1997). In conclusion, it remains controversial whether there is a biological tendency to prefer foods with specific macronutrient distribution across the menstrual cycle.

4.2 Hormonal contraceptives and food intake

In comparison with endogenous ovarian hormones, exogenous hormones used in the form of hormonal contraception are less investigated in the field of food intake research, possibly due to the methodological challenges. However, it has been speculated that they have potential to influence appetite and food intake (Davidsen et al. 2007), given that the weight gain has been reported to be one of the most common reasons to cancel the use of combined hormonal contraception (Rosenberg et al. 1998). In disagreement with this general experience of numerous women, no study to date has established the link between exogenous steroid hormones and increased body weight.

A closer look at the previous research investigating food intake of hormonal contraceptive users reveals that the findings are contradictory. Most studies have focused solely on orally ingested pills, thus there is a considerable lack of information related to other forms of hormonal contraception. Nevertheless, some studies have reported that women using oral contraceptives consumed significantly more fat (Eck et al. 1997) or calories (Wallace et al. 1987) compared to non-pill users while some studies have not observed differences in energy between these groups (McNeill et al. 1991; Pelkman et al. 2001; Massé et al. 2006).

The progestin component of combined oral contraceptive may be related to food intake. Side effects of oral contraceptives containing progestin that binds to the androgenic receptor, defined as androgenic progestin, encompass increased appetite. (Naessén & Hirschberg 2011, 1763.) This is consolidated by the evidence that antiandrogenic oral contraceptives decrease bulimic behavior in patients with bulimia nervosa (Naessén et al. 2007). Furthermore, progestins at high doses have been used successfully in the treatment cachexia, defined as involuntary weight loss induced by severe illness, and anorexia nervosa (Maltoni et al. 2001; Vanhoutte et al. 2016). In the case of healthy women, the proposed mechanism underlying the potential appetite-inducing effects of oral contraceptives is that they have been shown to suppress postprandial CCK release, which may lead to increased snacking and decreased post-meal satiety (Hirschberg et al. 1996). However, due to highly individual responses to pill's hormones (Nelson 2007) and challenges in assessment of the androgenicity of progestins (Lobo 1988), the exact mechanism in which oral contraceptives affects eating behavior is difficult to determine.

5 THE MENSTRUAL CYCLE AND SATIETY HORMONES

Previously aforementioned changes in food intake across the menstrual cycle have provoked discussion about the relationship between appetite-regulating hormones and ovarian steroid hormones. However, it has been previously investigated to a very limited extent, and results are plagued by inconsistency. Only a few studies focusing mainly on leptin and insulin have demonstrated fluctuations across the menstrual cycle, while ghrelin has not received similar attention. Therefore, studies related to these associations are highly needed to expand the understanding and draw more profound conclusions about the appetite regulation in women. (Townsend 2016.)

5.1 Changes of leptin during the menstrual cycle

The multifunctional role of leptin includes the stimulatory effect on the HPO-axis (Chehab 2014). Leptin regulates ovarian function, oocyte maturation and embryo development as well as implantation (Cervero et al. 2005). In fact, leptin levels of women are reported to be two or three-fold compared to those of men (Pérez-Pérez et al. 2015). In amenorrheic women with suppressed leptin levels, administration of leptin restored their menstrual cycle and fertility (Chou et al. 2011). In reference to these findings, it is very likely that leptin responds to fluctuating ovarian hormones across the menstrual cycle.

Ludvig et al. (2000) demonstrated for the first time that leptin concentration is significantly higher in the luteal phase compared to the follicular phase. Later, other studies have shown similar results (Wunder et al. 2006; Asimakopoulos et al. 2009; Ajala et al. 2013; Rafique et al. 2018). Ajala et al. (2013) found that the serum leptin was at the lowest level during the menstruation and the late luteal phase, and highest at the ovulation and day 21 of the luteal phase, whereas some studies have reported a peak during the pre-ovulatory phase (Hardie et al. 1997; Cella et al. 2000; Ahrens et al. 2014). Only a few studies have reported non-significant variation of leptin across the menstrual cycle (Teirmaa et al. 1998; Lin 1999; Stock et al. 1999). Overall, these results support the notion that progesterone and estradiol are crucial regulators of leptin during the normal menstrual cycle. It has been speculated that possible explanations for elevated leptin in the luteal phase could be that 1) the corpus luteum may be the source of leptin in the luteal phase, and 2) for the purpose of preparing the female body for the energy demand of pregnancy, leptin acts as a signal of energy balance and sufficient nutritional resources to guarantee successful reproduction (Cella et al. 2000; Tessier et al. 2013).

Leptin is suggested to have a dynamic relationship with hypothalamic-pituitary-ovarian hormones, estradiol and LH. Licinio et al. (1998) tested this hypothesis by collecting plasma from healthy women in different phases of menstrual cycle. They found significant synchronicity between the release patterns of LH, estradiol, and leptin, which may explain the interference in the HPO axis function in illnesses characterized by low leptin, such as anorexia nervosa (Licinio et al. 1998). LEP-Rs are identified in the pituitary (Jin et al. 1999; Popovic et al. 2001) and ovaries (Karlsson et al. 1997), which indicates that leptin has ability to stimulate HPO-axis directly (Pérez-Pérez et al. 2015). In addition to its direct effects, leptin might also regulate GnRH via indirect mechanisms by interneurons such as NPY and POMC mediating its actions (Czaja et al. 2002; Xu et al. 2012).

The relationship between leptin and HPO-axis is further strengthened by the findings from studies evaluating leptin levels of subjects with menstrual disturbances. Thong et al. (2000) compared leptin levels in two groups of elite athletes, either amenorrheic or healthy, to those of two groups of recreationally active women, either oral contraceptive users or naturally cycling. Regardless of menstrual status, they found that elite athletes had lower plasma leptin compared with both groups of recreational athletes, possibly due to significantly lower body fat. Hypoleptinemia was observed in amenorrheic athletes, corresponding to suppressed estradiol and lower caloric intake. In agreement with other studies, an increase in leptin during luteal phase was observed in healthy athletes. Ahrens et al. (2014) recorded lower luteal phase leptin levels in subjects with anovulatory cycles compared to those with normal cycles, irrespective of the energy intake and physical activity. They also deduced that leptin might be involved in the initiation of ovulation, given its concomitant surge with LH, confirming the previously suggested co-pulsatility between these two hormones. However, Thong et al. (2000) noted that the inconsistency in absolute rise of leptin indicates relatively wide interindividual variation. Additionally, it was highlighted that caution must be taken when interpreting these results, given that a single blood assay may not be able to indicate slight menstrual disturbances. (Thong et al. 2000).

The effect of hormonal contraceptives on leptin levels has been investigated less, but a few studies have shown that they have no influence (Castracane et al. 1998; Rechberger et al. 1999; Cella et al. 2000; Thong et al. 2000). However, a relatively new study of Fallah et al. (2012) reported a non-significant increase in leptin levels among combined oral contraceptive users compared to women with a normal menstrual cycle, suggesting that oral contraceptive use may induce production of free radicals stimulating leptin production (Fallah et al. 2012).

5.2 Changes of ghrelin during the menstrual cycle

Literature regarding associations between ghrelin and exogenous or endogenous female sex hormones is still in its infancy, and no study to date has demonstrated significant change in ghrelin during different phases of the menstrual cycle or hormonal contraception use in healthy women (Dafopoulos et al. 2009, Šramková et al. 2015). Dafopoulos et al. (2009) followed ghrelin levels of healthy premenopausal women during a whole menstrual cycle and found that AG and UnAG did not change significantly during the menstrual cycle. In accordance with Dafopoulos et al. (2009), Townsend (2016) observed no changes of AG across the menstrual cycle. On the other hand, Šramková et al. (2015) found the trend of decreasing ghrelin in the middle of the cycle, but it was non-significant.

There is suggestive evidence of relationship between ghrelin and estradiol, especially in patients with severe undernutrition or ovarian dysfunction. Synthetic estradiol, in the form of an oral contraceptive, increased ghrelin levels in anorexigenic subjects (Grinspoon et al. 2004) and in women with polycystic ovarian syndrome (Sagsöz et al. 2009). In healthy pre- and post-menopausal women, similar effect was not observed (Dafopoulos et al. 2010). Furthermore, suggestions between ghrelin and LH pulsatility have been provided, referring to the previous observations in rats (De Souza et al. 2004). Furuta et al. (2001) demonstrated that ovariectomized rats receiving estrogen replacement therapy responded to the ghrelin administration by suppression of LH pulse frequency. Given that ghrelin receptors are highly expressed in the same hypothalamic area where the release of GnRH takes place (Gnanapavan et al. 2002), it is reasonable to suspect that the link between ghrelin and disruptions in the LH release patterns exists (De Souza et al. 2004). For instance, elevated ghrelin levels in undernourished patients are consistent with suppressed release of GnRH, resulting in low estradiol (Grinspoon et al. 2004). However, the question remains unsolved whether sex hormones, the severe prolonged energy deficiency or other hormonal imbalances represent the cause of higher ghrelin levels.

Interestingly, the evidence obtained from animal studies significantly differ from above mentioned observations. The study of Matsubara et al. (2004) demonstrated that injection of estradiol decreased ghrelin levels in ovariectomized rats, which flatly contradicts the results of studies investigating both undernourished and healthy human population. Furthermore, Clegg et al. (2007) found that total ghrelin did not stimulate energy intake in rats after estradiol infusion, which indicates that estradiol may diminish the orexigenic actions of ghrelin. It is

noteworthy that these findings cannot be generalized directly to humans, but currently they represent the best information available.

5.3 Changes of fasting glucose and insulin across the menstrual cycle

Prior research confirms that female sex hormones and glucose metabolism have associations. Across the female lifespan, from puberty to pregnancy and menopause, ovarian hormones influence insulin sensitivity and glucoregulation (Brunz & Kemniz 2004; Pasqali 2017). Estradiol is known to reduce hepatic glucose production and alter gluconeogenic enzyme activity, leading to decreased fasting glucose levels (Godsland 1996; Mandour et al. 1977). Progesterone, in turn, may elevate insulin levels through direct action on pancreatic isles (Kalkhoff 1982).

In diabetic women, glucose levels tend to rise in the luteal phase (Goldner et al. 2004; Barata et al. 2013; Rani & Desai 2013). However, little research has been conducted to show changes across the menstrual cycle in healthy women, and they fall short of identifying consistent results. Some studies have observed a slight, non-significant increase (Bennal & Kerure 2013) or significant increase (Diamond et al. 1989) in fasting blood glucose during the luteal phase, whereas one study reported modest decrease of glucose levels during ovulation and the early luteal phase (Yeung et al. 2010).

Similarly, studies assessing fasting insulin across the menstrual cycle have not yielded consistent results. Some have reported increased levels during the ovulation and luteal phase, as well as positive associations with progesterone and estradiol (Yeung et al. 2010), while others have not found any significant alterations (Diamond et al. 1989). Insulin sensitivity, assessed by homeostasis model of insulin resistance (Yeung et al. 2010) or intravenous glucose tolerance test (Pulido & Salazar 1999), appears to be impaired during the luteal phase. Based on this impairment, it can be speculated that fasting insulin may be higher during the second half of the menstrual cycle, given that lower fasting insulin reflects higher insulin sensitivity (Fung et al. 2013). In conclusion, the mechanisms elucidating the relationship between ovarian steroid hormones and glucose metabolism remain to be unraveled. A couple of prospective suggestions, however, have been made. Among them, cyclic variations in insulin receptor binding and activity has gathered the most attention (De Firro et al. 1978; Moore et al. 1981).

The effects of hormonal contraception on glucose metabolism depend on the product and the type of the contraception. It has been speculated that recognized cardiovascular adverse effects

of combined oral contraceptives may be determined by either the dose of synthetic hormones or the androgenic properties of progestin contained in the pill (De Leo 2016). Higher androgenic activity has been shown to associate with insulin resistance (Cagnacci et al. 2009). However, the majority of studies suggest that insulin and glucose remain unchanged in women using combined oral contraceptives, irrespective of the contraceptive type (Wynn & Doar 1969; Burkman et al. 1992; Troisi et al. 2000; Biswas et al. 2001). Compared to women with non-hormonal contraception, Berenson et al. (2011) did not observe significant differences in fasting glucose and insulin. In contrast, the study of Kim et al. (2002) demonstrated that oral contraceptive use was associated with lower glucose and higher insulin compared with non-using women. Referring to lower glucose levels, they concluded that the current use of oral contraception has the potential to lower the risk of diabetes. However, inconsistent findings may be explained by inability of evaluating confounder factors, and a small number of participants (Kim et al. 2002) as well as varying androgenicity of progestin between studies (Cortés & Alfaro 2014, Cagnacci et al. 2009).

5.4 Associations between satiety hormones and changes of food intake and cravings across the menstrual cycle

As previously indicated, the luteal phase calorie-dense food cravings and increased food intake appear to be paradoxical to the hypothesis that leptin rises during the luteal phase, given the appetite-suppressing properties of leptin. In fact, limited human studies have shown conflicting results related to leptin and modification of food intake, including food preferences and cravings (Krishnan et al. 2016). Macedo and Diez-Garcia (2014) found that leptin increased stress-induced sweet-craving, whereas Karhunen et al. (1998) demonstrated the inverse association between leptin and both sugar and fat preference in obese women.

Paolisso et al. (1999) investigated the relationship between changes of leptin and food intake in the context of the menstrual cycle. While the typical patterns of both leptin and food intake were identified across the menstrual cycle, correlation between them was not observed during any of the phases. Later, Gil et al. (2009) and Chung et al. (2010) confirmed this finding, indicating no significant correlations between leptin and food intake during the menstrual cycle. In contrast, the study of Krishnan et al. (2016) was not able to demonstrate variation in leptin between phases, but instead succeeded to show an inverse association between leptin and sweet food intake, regardless of the menstrual cycle phase. They classified women in two subgroups, low- and high-cravers. The group with higher cravings had higher estradiol and estradiol in

relationship with leptin. It was concluded that these differences in cravings likely reflect underlying endocrine differences rather than only leptin (Krishnan et al. 2016), which may also account for inconsistencies between studies.

Supporting the well-known nature of ghrelin in appetite regulation, it has been demonstrated by Chao et al. (2017) that ghrelin also predicts food cravings. In the perspective of ovarian steroid hormones, AG failed to explain the changes in energy intake across the menstrual cycle in the study of Townsend (2016). However, it was found that perceived fullness was elevated during the luteal phase, reflecting fluctuating sensitivity to ghrelin across the menstrual cycle (Townsend 2016). In terms of taste sensitivity, Shin et al. (2010) have demonstrated that ghrelin is localized in taste cells of mice and has the potential to modify sour and salty tastes. Barbosa et al. (2015) found an inverse association between ghrelin and sour taste in humans, which suggests that high ghrelin may reduce acid taste perception. In addition, reduced sensitivity to acid taste during the luteal phase was observed, which may be one contributing factor to increased prevalence of cravings, given that sweet foods typically have a sour flavor (Barbosa et al. 2015).

6   PURPOSE OF THE STUDY

The purpose of this study was to investigate associations between the menstrual cycle phases or the hormonal contraceptive use, food intake and cravings. The primary focus was to 1) examine if leptin, ghrelin and insulin, referred as satiety hormones, change across the fluctuating estradiol and progesterone, referred to as ovarian steroid hormones, and 2) examine if there are associations between either satiety hormones and food intake or ovarian steroid hormones and food intake. The secondary focus was to examine associations between fasting glucose, food intake, cravings, and the ovarian steroid hormone levels. The research questions and hypotheses of the present study are:

Question 1. Does the menstrual cycle or hormonal contraceptive use influence self-reported energy intake, macronutrients, and cravings?

Hypothesis 1. Self-reported energy intake and cravings may be higher during the luteal phase and lower at ovulation, mainly because of progesterone and estradiol (Gilbert & Gillman 1956; Bancroft et al 1988; Dye & Blundell 1997; Hirschberg et al. 2012). The distribution of macronutrients may vary across the menstrual cycle (Dye & Blundell 1997; Hirschberg et al. 2012; Gorczyga et al. 2006). Hormonal contraceptives are unlikely to have a significant impact on energy intake, macronutrients and cravings (Procter-Gray et al. 2008; McNeil et al. 1991).

Question 2. Does the menstrual cycle or hormonal contraceptive use affect total ghrelin, leptin, insulin, or glucose concentrations?

Hypothesis 2. The menstrual cycle has no effect on total ghrelin (Dafopoulos et al. 2009; Šramková et al. 2015; Townsend 2016). The association between hormonal contraceptive use and ghrelin has not been studied to date in healthy women. Leptin may rise around the ovulation (Cella et al. 2000; Ahrens et al. 2014; Hardie et al. 1997) and in the luteal phase (Ludvig et al. 2000; Thong et al. 2000; Wunder et al. 2006; Asimakopoulos et al. 2009; Ajala et al. 2013; Rafique et al. 2018). Hormonal contraceptive use is unlikely to have effect on leptin (Castracane et al. 1998; Rechberger et al. 1999; Cella et al. 2000; Thong et al. 2000).

Fasting insulin (Yeung et al. 2010) and fasting glucose (Diamond et al. 1989; Barata & Bennoit 2013) may be higher during the luteal phase. Hormonal contraceptive use has no effect on fasting insulin and glucose levels (Wynn & Doar 1969; Burkman et al. 1992; Troisi et al. 2000; Biswas et al. 2001).

Question 3. Are satiety hormones or fasting glucose associated with energy and macronutrient intake, or cravings?

Hypothesis 3.

Despite the general agreement that leptin is negatively associated with energy intake and appetite (Matson et al. 1997; Karhunen et al. 1997; Bado et al. 1998; Elmquist et al. 1999, Klok et al. 2007; Myers et al. 2010; Krishnan et al. 2016; Hussain & Khan 2017), in respect of the menstrual cycle, associations may not be detected (Paolisso et al. 1999; Gil et al. 2009; Chung et al. 2010) possibly due to endocrine interactions (Krishnan et al. 2016). Ghrelin is positively associated with energy intake and appetite (Wren et al. 2001; Cummings et al. 2005; Druce et al. 2005; Cummings & Overduin 2007), including cravings (Chao et al. 2017). To date, it has not been studied whether fasting insulin or glucose has effects on energy intake, macronutrients or cravings.

7 METHODS

7.1 Subjects

Twenty-nine healthy women between ages 18 and 40 were recruited to study through posting lists, social media, advertisements in gyms and sport halls, and orally. They were distinguished in two groups based on their hormonal status: women who had never used hormonal contraception (N), and women who had used hormonal contraception (H) at least for year. The initial sample consisted of 30 women, 16 of whom in the N-Group and 14 in the H-group. During the process of the study, five subjects in the H-group withdrew from the study due to personal reasons. Anthropometric data of N-group in the follicular phase measurement point and H-group in the first active phase measurement point are presented in the Table 1.

TABLE 1. Anthropometric data (Mean ± SD) of non-hormonal contraception (N) group and hormonal contraception (H) group at follicular or first active phase. BMI = Body mass index

Group	n	Age (years)	Height (cm)	Weight (kg)	BMI (kg/m²)	Body fat (%)
N	16	26.2 ± 4.4	167.1 ± 5.7	66.6 ± 6.9	23.9 ± 2.5	22.1 ± 6.4
H	9	22.9 ± 2.4	171.6 ± 5.3	60.9 ± 4.5	21.0 ± 1.4	19.6 ± 2.9

Inclusion criteria for participation in both groups required subjects to be at least recreationally active and have a BMI of less than 30 kg/m² and more than 18 kg/m². "Recreationally active" was defined as a physically active person with some athletic goals. Although participation in competition was not required, subjects with competitive purposes were not excluded from the study. Exclusion criteria included current pregnancy or lactation, amenorrhea, conditions affecting ovarian function, endocrine disorders, chronic diseases, or medications affecting exercise function. In the H-group, subjects were required to be using the hormonal contraception for a minimum of one year prior to study. Accepted forms of hormonal contraception were oral pills and intrauterine devices including synthetic estradiol and progestin. Hormonal contraception used by the H-group are presented in the Table 2.

TABLE 2. Hormonal contraceptive products used in the study. EE = Ethinyl Estradiol

Product	Type	Hormone content
Yaz	Monophasic combined pill	Drospirenone, EE
Zoely	Monophasic combined pill	Nomegestrol acetate, EE
Stefaminelle	Monophasic combined pill	Drospirenone, EE
Yasmin	Monophasic combined pill	Drospirenone, EE
Nuvaring	Vaginal ring	Etonogestrel, EE
Tasminetta	Monophasic combined pill	Drospirenone, EE

The training background of the subjects consisted of jogging, running, triathlon, orienteering, cross-country skiing, CrossFit, and ball games. Regarding the level of sport, subjects remarkably differed from each other: some subjects engaged in a variety of recreational sports, whereas other subjects were competing at national, or even international level. However, all subjects were highly active and participated in both endurance and strength training, albeit in varying proportions.

Prior to final inclusion in the study, each subject candidate completed a health questionnaire and Low Energy Availability in Females Questionnaire (LEAF-Q), which is a screening tool designed to identify the risk for female athlete triad (FAD). LEAF-Q includes questions regarding previous menstrual cycles, injuries, and gastrointestinal symptoms, which could possibly reflect clinical manifestations such as eating disorders, amenorrhea, and osteoporosis (Loucks et al. 2007). These conditions lie at the heart of FAD, although the diagnosis can be made based on the wide spectrum of symptoms related to low energy availability (Nazem & Ackerman 2012; De Souza et al. 2014.) LEAF-Q is a reliable and valid method to detect the athletes at risk of FAD, with a sensitivity of 78% and specifity of 90% (Melin et al 2014).

Prior to implementation of the study, the research plan was sent to the Ethical Committee at the University of Jyväskylä, where the methodology was approved. Subjects were provided detailed information regarding measurements and study procedures, including the right to drop out from the study at any time without giving any reason. Once the written and oral clarification was given, subjects signed an informed consent document before prior to the start of study.

7.2 Study design

This study was a part of a larger project "Exercising Women" in which the purpose was to investigate the effect of menstrual cycle or hormonal contraception on exercise performance and general health. Thus, in addition to the protocol described above, subjects underwent standardized maximal exercise tests assessing both strength and endurance performance during each experimental testing session. Subjects were required to adhere their usual training programs throughout the period of investigation, and refrain from vigorous activities on the day before testing.

Both groups completed four identical testing sessions (Figure 8). The N-group participated in sessions during the menstrual phase, the follicular phase (7–11 days from the onset of menstruation), ovulation and the luteal phase (determined as 7 days after ovulation). The ovulation was detected by daily identification of the LH surge using an internationally marketed ovulation (urine) test. For the H-group, the same experimental testing sessions were carried out once during withdrawal bleeding, twice during the active pill phase (first test + 7 days; first test + 14 days) and once during the inactive pill phase (days 22–24). For both groups, the order of testing was randomized to minimize order effects and balanced with the respect to the cycle phase. On each visit, subjects completed the same measurements that consisted of venous blood samples in a fasted state and body composition measurements. The timing of measurements was not standardized due to scheduling issues; however, all tests were performed in the morning between 07:00 AM and 10:00 AM. Subjects were asked to complete a three-day prospective nutritional diary around each testing session.
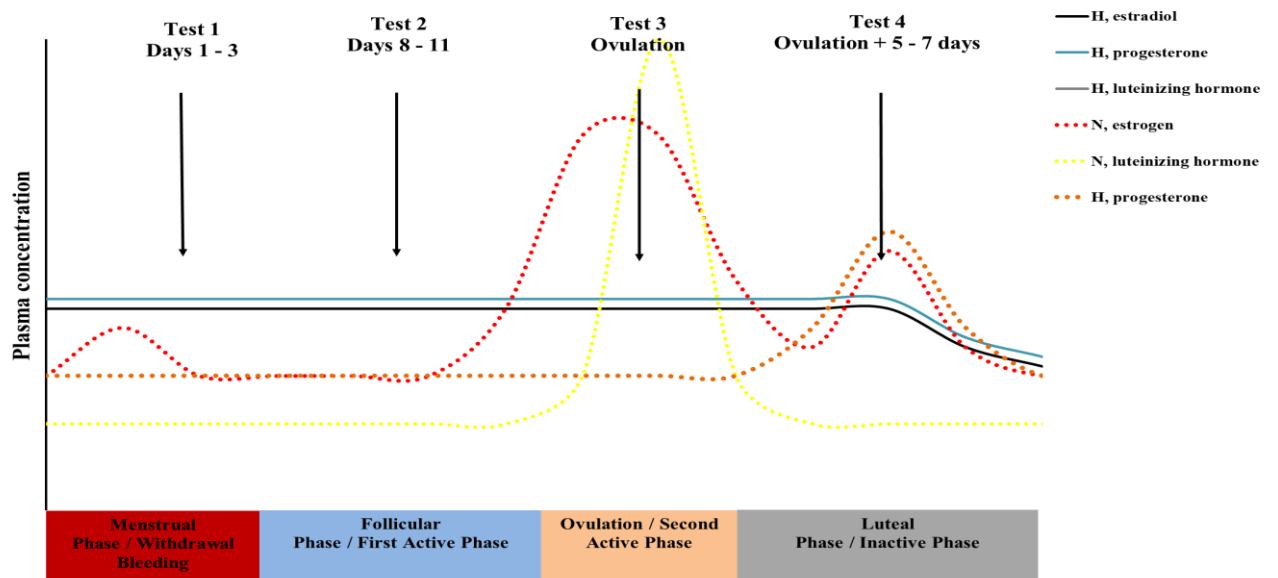
FIGURE 8. Measurement points for the N-group and the H-group. Each measurement point included blood and body composition assessment tests in a fasted state, and collection of three-day prospective nutritional diary around each testing session.

7.2.1 Nutritional assessment

For the purpose of examining the dietary intake and cravings, subjects recorded their food intake with a set of 3-day estimated dietary record around each measurement session. When used adequately and the number of recording days is sufficient, the estimated dietary record has acceptable validity (Chinnock 2006; Yang et al. 2010; Putz et al. 2019) and reliability (Tremblay et al. 1988; Putz et al. 2019).

Subjects were given three options for recording period: 1) the day prior, the testing day, and the following day, 2) two days prior to testing and the testing day, or 3) the testing day and two following days. Altogether, habitual food intake was recorded for each subject on 12 days during the study. Written instructions for recording were given to each subject individually, with an emphasis on accuracy. Subjects were asked to record all the consumed food, beverages, and supplements, and to keep their habitual diet as usual as possible during the days of recording. To avoid memory issues, it was recommended that subjects record their meals immediately after eating. Subjects were instructed to estimate the amount of each food by using household measuring cups and spoons, and a kitchen scale was recommended for improved accuracy. If estimating or weighing was not possible, subjects were given the option of photographing meals with a smart phone and to send to researchers.

The recording template form included a column for each eating situation (eating location, such as home or lunch canteen, and time) and row for each product or food. Subjects were instructed to list the quality of food products (such as skimmed milk, oat meal made with milk, tuna canned in oil), commercial names (such as greek yoghurt, light snack -sausage), producer (such as Atria, Fazer, Valio, Rainbow), preparation method ("potato, cooked", "egg, fried", "apple, peeled"), fat percentage and sugar or sweetener content. The recording template also included an open-ended question, where subjects were asked to report cravings, regardless of whether food was eaten or not.

To quantify daily nutrition composition, the food diaries were analyzed with the National Food Composition Database in Finland (Fineli) by the same researcher. If a food or product was not found in the database, it was replaced by composing similar ingredients to achieve same macronutrient and energy content. For statistical analysis, average kilocalories, grams of fat, grams of protein and grams of carbohydrate, were calculated from each three-day nutritional diary around each measurement point. Cravings were classified to yes (1) or no (2), and the number of yes-answers was calculated. "Yes" included sweet, salty, soda drinks and notes of experiencing more hunger than usual. "No" included mentions of absence of cravings or no notes about cravings.

7.2.2   Verification of menstrual cycle phases

The menstrual cycle phases were estimated from the first menstrual bleed. Ovulation was identified by a combination of counting days from menstruation, depending on the typical length of cycle of each subject, and the luteinizing hormone surge detection method using ovulation test kit (Dipro, LH Ovulation Strip). (De Jonge et al. 2019.)

Subjects were given written instructions to use and interpret ovulation test. They were instructed to start using the test four days prior to halfway of their cycle, counted from the average cycle length, and schedule test at the same time each day, avoid excessive liquid intake two hours prior to test and not to use first urine in the morning. The subject was asked to contact research staff immediately after positive ovulation test to be measured within 24 hours after the detection of ovulation. If the ovulation was not identified, the test day was scheduled by using the counting method. The date of the luteal phase measurement was counted from approximately seven days after positive result from ovulation test.

7.2.3 Anthropometrics and body composition

Anthropometric measurements included height and body composition assessment. The height of each subject was measured using standard protocol. Body composition was assessed with a multifrequency bioelectrical impedance analyzer (InBody 720; Biospace, Seoul, Korea) in a fasted state (12h) and in underwear. To avoid changes in eating behavior, the feedback of anthropometrics remained concealed from the subject until all four testing sessions were completed.

7.2.4 Blood assessment

The subjects arrived at the blood assessment in a fasted state (12h) between 7.00 and 9.00 in each testing session. Blood was drawn into 7ml Vacuette serum tubes and 4 ml K2EDTA tubes with sterile needles from the antecubital vein in a sitting position by a qualified lab technician. Samples in Vacuette serum tubes were allowed to sit for 15 min before centrifugation. Both samples were centrifugated at 2000g for 10 minutes and frozen at -20°C until the determination of estradiol (E2), progesterone (P4), leptin, ghrelin, insulin and glucose. Insulin, estradiol and progesterone analyses were performed using chemical luminescence techniques (Siemens Immulite 2000XTi). and glucose analysis by Thermo Konelab 20xP. Leptin was analyzed with the Biovendor Human Leptin ELISA, and total ghrelin with the Biovendor Human Unacylated Ghrelin Easy Sampling ELISA from plasma after incubation in room temperature for 2 hours. The sensitivity of serum hormones and the inter assay coefficients of variations are illustrated in the Table 3.

TABLE 3. The sensitivity and the inter-assay coefficients (CV) of variations for serum hormones. P4 = Progesterone, E2 = Estradiol

	Sensitivity	**CV**
E2	55.0 pmol/l	6.7 %
P4	0.3 ng/ml	9.7 %
Leptin	0.2 ng/ml	4.2 %
Ghrelin	10 mg/l	6.8 %
Insulin	2 mU/l	5.1 %
Glucose	0.1 mmol/l	1.4 %

7.2.5   Statistical Analysis

Statistical analyses were conducted in IBM SPSS Statistics 26 computer software and figures were graphed with Microsoft Excel 2010. One-way ANOVA was used to compare means between the N- and H-groups in different measurement points. Post-hoc tests were used to explore time effects using Bonferroni's correction for multiple comparisons. Data are reported and displayed as means and standard deviations (SD). Statistical significance was set at $p \leq 0.05$ but trends were explored with post-hoc tests when $p \leq 0.1$ for main effects.

Between-group differences in cravings were evaluated with Chi Square test. Related-Samples Cochran's Q Test was used to examine changes in cravings across the measurement points, and hormone levels across cravings were evaluated with non-parametric Kruskal-Wall's test. Associations between hormones and dietary variables were identified with Spearman's correlations. Means and standard deviations were calculated using standard methods. A statistician was consulted when necessary. The significance for all tests was set at $*p<0.05$, $**p<0.01$ and $***p<0.001$. All data are presented as mean±standard deviation.

8   RESULTS

To gain more comprehensive understanding about the independent effects of ovarian steroid hormones and satiety hormones, the change in body mass and fat percentage across measurement points was examined first (Table 4). The N-group had 9 % higher body mass in the menstrual phase and the follicular phase compared to the corresponding phases in the H-group. Between-group changes are presented in the Figure 9. Body mass and fat percentage remained stable during the study period in the N-group, whereas body mass was significantly higher in the inactive phase compared to the withdrawal bleeding (p=0.014) and the first active phase (p=0.003) in the H-group.

TABLE 4. Between-group differences (mean ± SD) in mean body mass and fat percentage. * Presents significant between-group difference (p < 0.05). Significant differences in bold. (N: n=16, H: n=9)

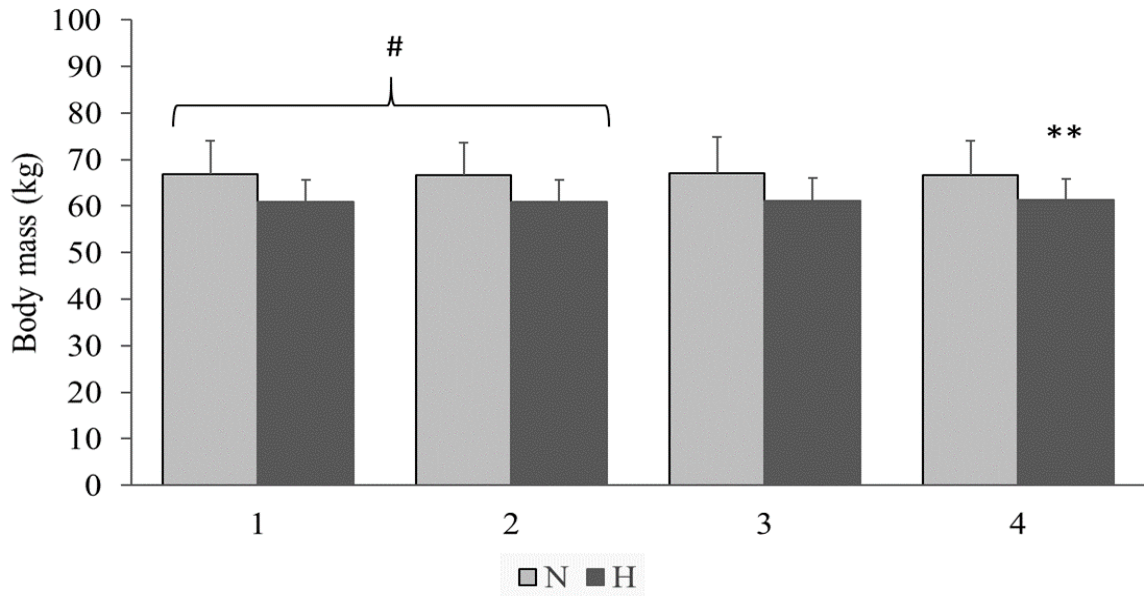|	Menstrual Phase/Withdrawal bleeding		P-value	Follicular/ Active Phase		P-value	Ovulatory/ Active Phase		P-value	Luteal/ Inactive Phase		P-value
Group	N	H		N	H		N	H		N	H	
Body mass (kg)	67±7.9	61±4.6	**0.035***	67±7.9	61±4.7	**0.043***	67±8.1	61±4.9	0.054	67±7.8	61±4.5	0.056
Fat percentage (%)	23±7.2	19±2.9	0.35	23±7.0	20±3.0	0.29	22±6.8	20±3.2	0.5	22±7.0	20±2.8	0.41

FIGURE 9. Changes (mean ± SD) in body mass across the measurement points. # Presents significant between-group difference (p < 0.05), # present between-group difference, * presents for a significant difference to withdrawal bleeding (1) and first active phase (2). ** p<0.01. 1 = Menstrual Phase/Withdrawal Bleeding, 2 = Follicular Phase/First Active Phase, 3 = Ovulation/Second Active Phase, 3 = Luteal Phase/Inactive phase (N = 16, H = 9)

8.1 Between-group differences in hormones

Mean (±SD) hormone levels in the N- and the H-group are presented in Table 5. There were no differences in mean hormone levels between groups, except for estradiol and progesterone. The N-group exhibited higher estradiol values in all phases compared to the H-group. Estradiol was 140 % higher in the follicular phase compared to the active phase (p=0.047), 199 % higher in ovulation compared to active phase (p=0.021), and 264 % higher in the luteal phase compared to the inactive phase (p=0.001). Mean progesterone was 193 % higher in the ovulation compared to the active phase (p=0.011) and 1029 % higher in the luteal phase compared to the inactive phase (p=0.001).

TABLE 5. Mean (±SD) hormone levels in the N- and the H-group across the measurement points. * Presents significant between-group difference (p < 0.05). Significant differences in bold. E2 = Estradiol, P4 = Progesterone, L = Leptin, GR = Ghrelin, I = Insulin, GL = Glucose (N: n=6, H: n=9)

	Menstrual Phase/ Withdrawal bleeding		P-value	Follicular/ Active Phase		P-value	Ovulatory/ Active Phase		P-value	Luteal/ Inactive Phase		P-value
Group	N	H		N	H		N	H		N	H	
E2 (pmol/L)	316±214	244±208	0.662	516±409	215±161	**0.047***	677±483	233±280	**0.021***	669±231	184±100	**0.001***
P4 (pmol/L)	1.8±1.7	1.1±0.6	0.206	1.0±0.5	1.1±0.5	0.786	4.1±2.7	1.4±1.1	**0.011***	15.8±7.9	1.4±1.1	**0.001***
L (ug/L)	6.8±4.0	8.3±7.4	0.509	7.3±5.4	8.0±7.8	0.777	8.5±6.1	8.2±7.6	0.929	7.8±5.2	8.4±6.5	0.811
GR (ng/L)	239±72	211±107	0.459	248±68	208±101	0.266	210±75	217±139	0.88	228±74	212±136	0.72
I (mIU/L)	3.0±1.9	3.1±3.0	0.955	3.1±2.9	3.7±2.8	0.665	3.9±3.6	4.7±2.9	0.595	3.5±3.1	3.1±2.5	0.794
GL (mmol/L)	5.0±0.3	4.8±0.4	0.139	5.1±0.4	4.8±0.5	0.416	4.9±0.5	4.9±0.5	0.84	4.9±0.4	4.9±0.3	0.913

For either of the groups, no changes in ghrelin, insulin or glucose were found across the menstrual cycle. In the N-group, significant phase effect to leptin was observed. Leptin was 25% higher at ovulation (p=0.010*) and 9% higher during the luteal phase (p=0.023*) compared to the menstrual phase. In comparison with the follicular phase, leptin was 16% higher at ovulation (p=0.023*) and 7% higher during the luteal phase (p=0.048*) (Figure 10).
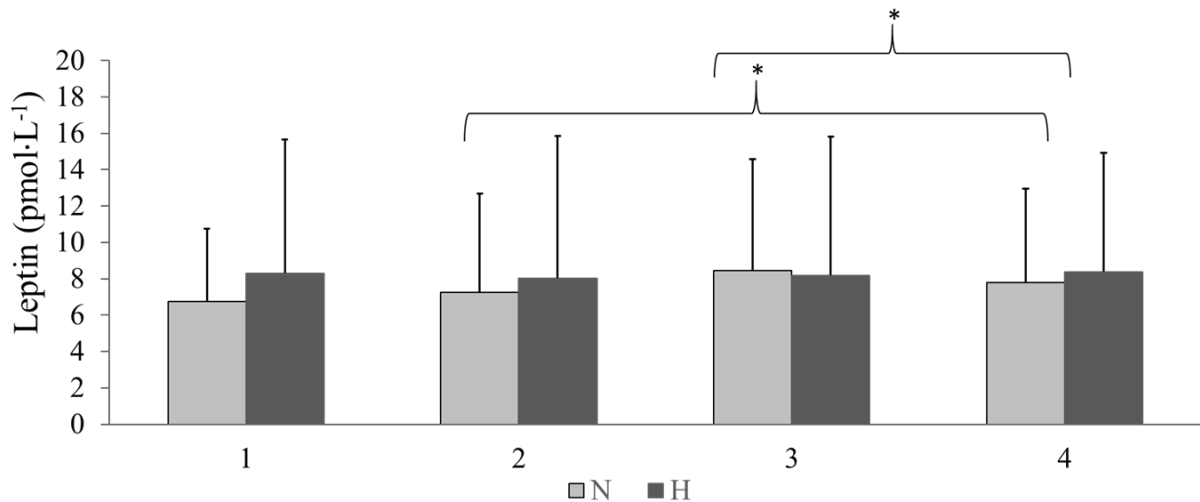
FIGURE 10. Changes (mean ± SD) in leptin across the measurement points. * Presents for a significant main effect of time. 1 = Menstrual Phase/Withdrawal Bleeding, 2 = Follicular Phase/First Active Phase, 3 = Ovulation/Second Active Phase, 3 = Luteal Phase/Inactive phase (N: n=16, H: n=9)

8.2 Between-group differences in dietary intake and cravings

Absolute and relative dietary intake are illustrated in Table 5 and Table 6. Between-group differences were not observed in absolute dietary intake However, in relation to body mass (kcal/kg·day), energy intake of the H-group was 32% higher during the withdrawal bleeding, 29% higher during the second active phase and 17% higher in the inactive phase compared to the menstrual phase, ovulation and the luteal phase of the N-group. Carbohydrate intake per body mass of the H-group was 28% higher in the withdrawal bleeding, 30% higher in the second active phase and 24% higher in the inactive phase compared to the N-group. Fat intake per body mass was 38% higher in the withdrawal bleeding of the H-group compared to the menstrual phase in the N-group. There was no variation in either absolute or relative dietary intake between phases of the menstrual cycle or the hormonal contraceptive use.

TABLE 5. Mean (±SD) absolute dietary intake in the N- and the H-group across the measurement points. E = Energy, C = Carbohydrates, F = Fat, P = Protein (Mean ± SD) (N: n=16, H: n=9)

	Menstrual Phase/ Withdrawal bleeding		P-value	Follicular/ Active Phase		P-value	Ovulatory/ Active Phase		P-value	Luteal/ Inactive Phase		P-value
	N	H		N	H		N	H		N	H	
E (kcal)	2377±644	2768±500	0.133	2366±530	2467±515	0.652	2285±511	2664±709	0.150	2276±375	2510±384	0.155
C (g)	259±79	307±60	0.130	262±74	273±61	0.706	247±67	301±91	0.117	251±55	294±44.0	0.062
F (g)	88±27	105±30	0.186	88±33	91±29	0.798	85±5.6	100±34	0.208	85±20	84±18	0.894
P (g)	112±39	119±39	0.699	108±29	109±27	0.890	110±39	109±30	0.936	102±27	110±36	0.532

TABLE 6. Mean (±SD) dietary intake in relation to body mass in the N- and the H-group across the measurement points. * Presents significant between-group difference ($p < 0.05$). Significant differences in bold. E = Energy, C = Carbohydrates, F = Fat, P = Protein (Mean ± SD) (N: n=16, H: n=9)

	Menstrual Phase/Withdrawal Bleeding		P-value	Follicular/ Active Phase		P-value	Ovulatory/ Active Phase		P-value	Luteal/ Inactive Phase		P-value
	N	H		N	H		N	H		N	H	
E (kcal/kg·day)	34±13	45±14	**0.021***	36±9	41±9	0.241	34±7	44±13	**0.032***	35±6	41±7	**0.022***
C (g/kg·day)	3.9±1.2	5.0±0.8	**0.028***	3.8±1.6	4.4±1.6	0.218	3.7±1.0	4.8±1.6	**0.031***	3.8±0.9	4.7±0.7	**0.013***
F (g/kg·day)	1.3±0.5	1.8±0.5	**0.049***	1.5±0.4	1.8±0.6	0.254	1.3±0.4	1.7±0.6	0.072	1.4±0.4	1.5±0.3	0.239
P (g/kg·day)	1.6±9.7	1.9±0.7	0.187	1.6±0.4	1.8±0.4	0.386	1.6±0.5	1.8±0.5	0.532	1.5±0.4	1.8±0.4	0.212

Cravings were reported in both groups. There was a significant between-group difference in cravings during the menstrual phase compared to the withdrawal bleeding (p=0.017*) and during the follicular phase compared to the first active phase (p=0.011*) (Figure 11).
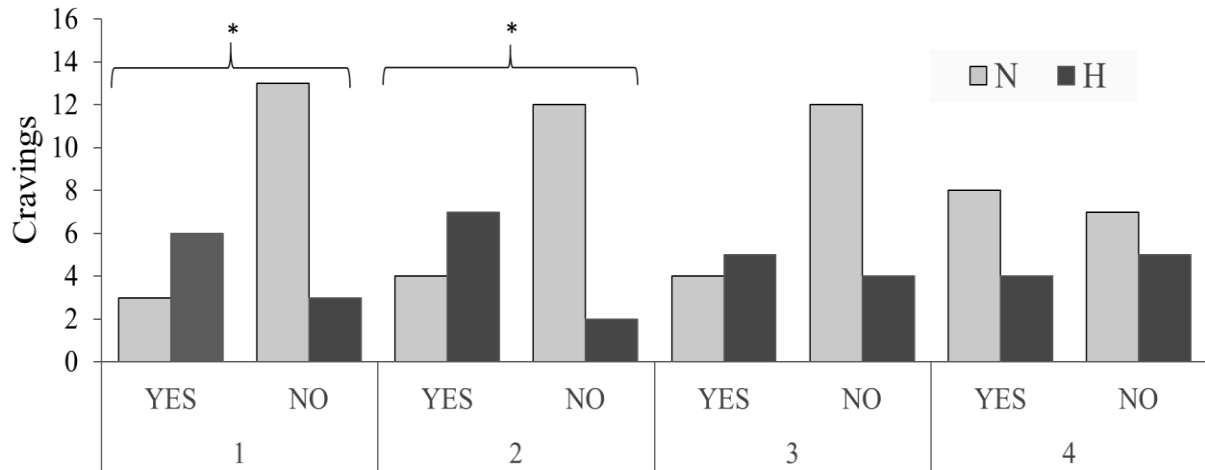
FIGURE 11. Between-group differences in cravings. * Presents significant between-group difference (p < 0.05) 1 = Menstrual phase / Withdrawal bleeding, 2 = Follicular phase / First active phase, 3 = Ovulation / Second active phase, 4 = Luteal phase / Inactive phase (N: n=16, H: n=9)

Kruskal-Wallis test was conducted to examine the within-group differences in hormones across experienced cravings. In the N-group, no significant differences were found except for progesterone in the follicular phase (Figure 12) (Test Statistic 5.90, p=0.015). In the H-group, the significant differences were found in progesterone in the withdrawal bleeding (Test Statistic 4.27, p=0.039) (Figure 13) and estradiol in the second active phase (Test statistic 4.86, p=0.027) (Figure 14).

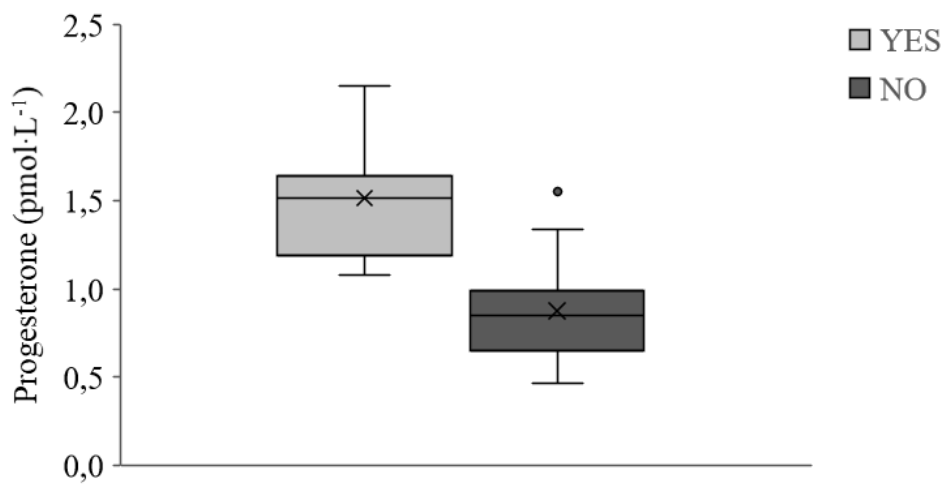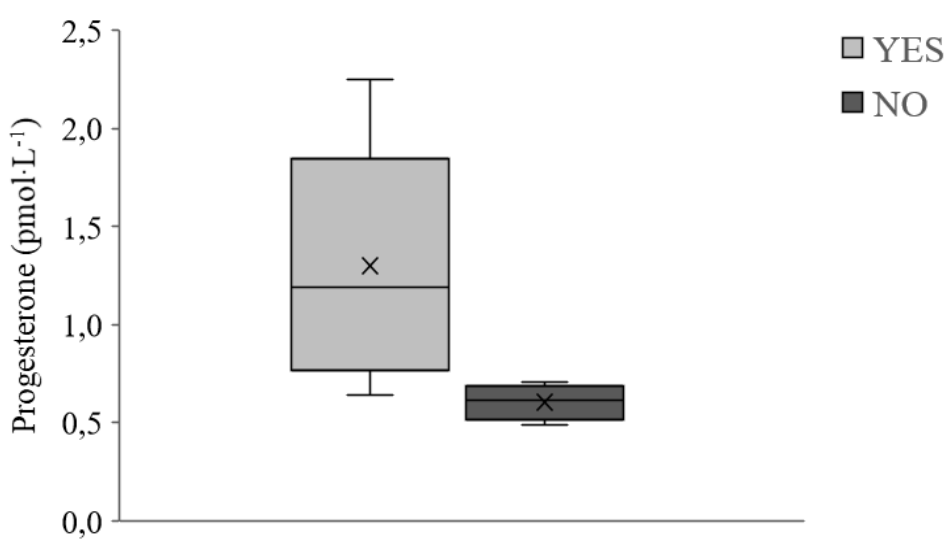**FIGURE 12**. Progesterone across cravings in the follicular phase, N-group (n=16)

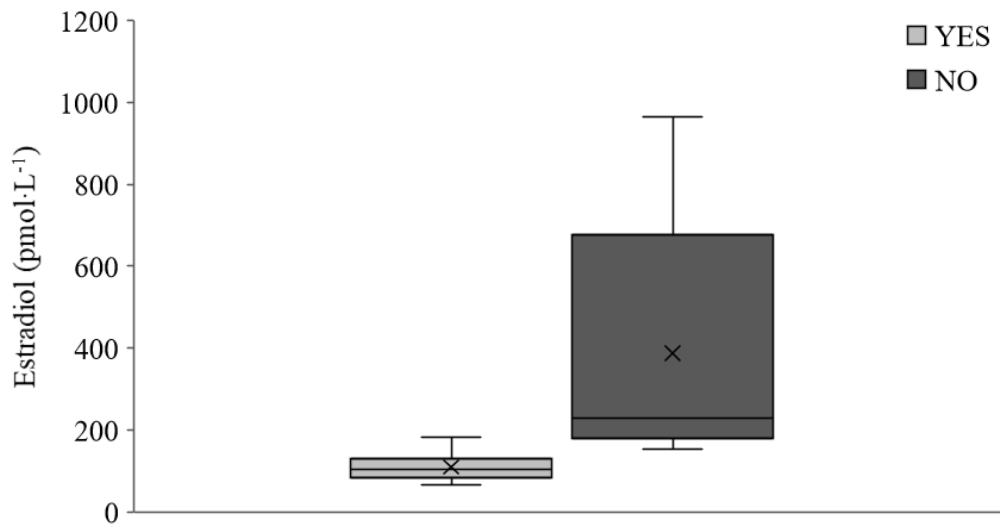**FIGURE 13.** Progesterone across cravings in the withdrawal bleeding, H-group (n=9)

FIGURE 14. Estradiol across cravings in the second active phase, H-group (n=9)

8.3 Associations between hormone levels and dietary intake

Associations between hormone levels and dietary variables are presented by the Spearman's correlation. All correlations across the measurement points in the N-group are presented in the Table 6. Leptin correlated negatively with protein intake in the luteal phase (Figure 15) and insulin correlated negatively with protein intake at ovulation (Figure 16). For glucose, positive correlations were found with menstrual phase energy intake ($r = 0.558$, $p < 0.05$) and carbohydrate intake ($r = 0.653$, $p < 0.05$) and follicular phase carbohydrate intake ($r = 0.704$, $p < 0.01$).

TABLE 6. Correlation coefficients (r -values) between hormone levels and dietary intake, N-Group (n=16). Significant correlations in bold. 1 = Menstrual Phase, 2 = Follicular phase, 3 = Ovulation, 4 = Luteal phase

	Energy				Carbohydrate				Fat				Protein			
	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
P4	-0.093	0.486	0.002	0.079	-0.197	0.352	0.011	0.211	0.115	0.431	0.415	0.243	-0.190	0.034	-0.081	-0.507
E2	0.218	-0.446	-0.490	-0.071	0.15	-0.439	-0.464	0.075	0.329	-0.2	0.134	-0.121	0.054	-0.219	-0.508	-0.039
L	0.336	0.037	-0.0226	-0.235	0.095	0.345	0.033	0.073	-0.081	-0.064	-0.022	-0.152	0.512	-0.240	-0.424	**-0.710****
GR	-0.292	0.064	-0.174	-0.099	-0.209	-0.007	-0.363	-0.446	-0.248	0.112	-0.116	0.077	0.257	0.073	0.200	0.459
I	0.172	-0.166	-0.490	-0.046	0.084	0.027	-0.349	0.132	0.309	0.059	-0.240	-0.421	-0.08	-0.406	**-0.741****	0.421
GL	0.558*	0.4	0.117	0.364	**0.653***	**0.704****	0.361	0.459	0.337	0.066	-0.037	0.053	0.168	-0.020	-0.106	-0.137

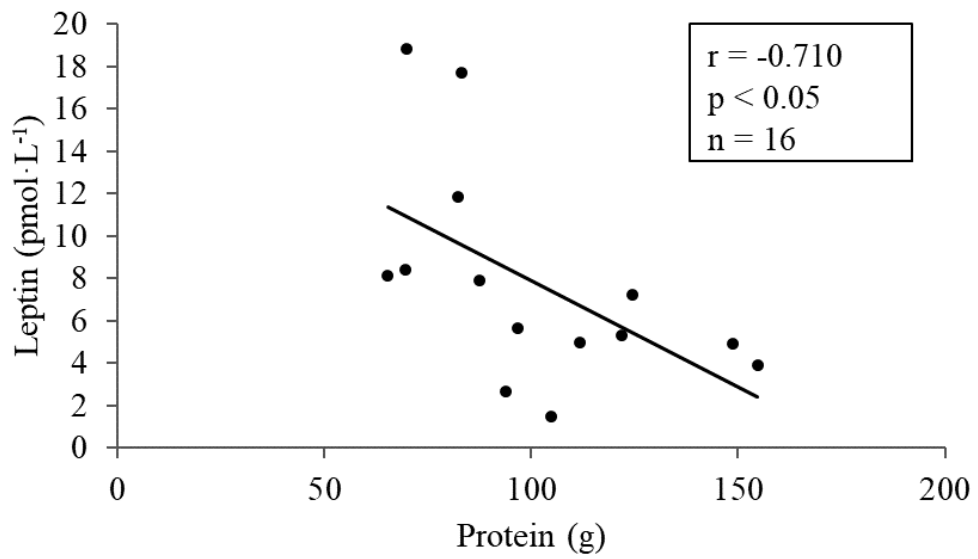r = Spearman's correlation coefficient

FIGURE 15. The correlation between leptin and protein intake in the luteal phase, N-group.
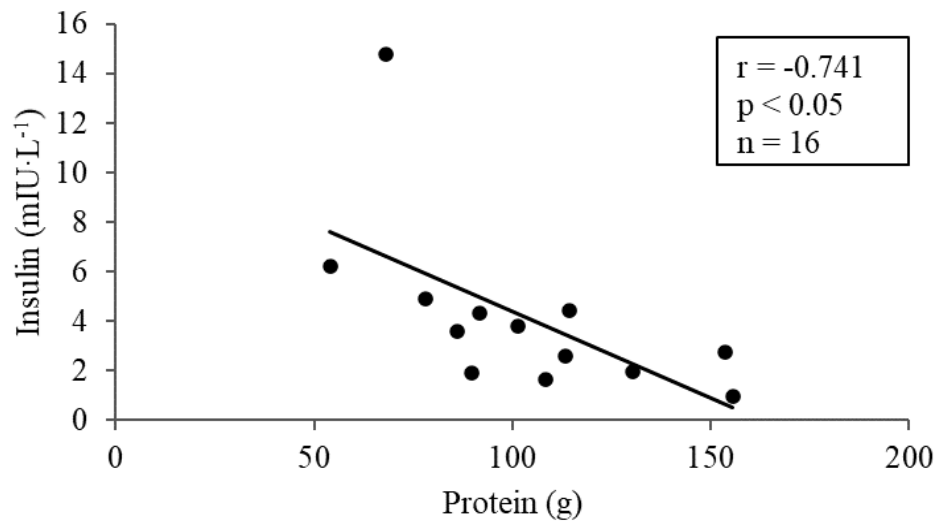

FIGURE 16. The correlation between insulin and protein intake at ovulation, N-group

Correlations across the measurement points in the H-group are presented in the Table 7. In the H-group, progesterone correlated positively with energy intake in the second active phase (r = 0.678, p < 0.05) (Figure 14) and with fat intake in the first active phase (r = 0.683, p < 0.05) and the second active phase (r = 0.683, p < 0.05). In the second active phase, positive associations were observed between insulin and energy intake (r=0.667, p < 0.05), insulin and fat intake (r=0.683, p < 0.05), estradiol and energy intake (r = 0.767, p < 0.05), and estradiol and carbohydrate intake (r = 0.833, p < 0.01). In the inactive phase, positive correlation between estradiol and protein intake were observed (r=0.667, p < 0.05). In the first active phase, glucose correlated positively with carbohydrate intake (r = 0.667, p < 0.05) and protein intake (r = 0.883, p < 0.05).

TABLE 7. Correlation coefficients (r-values) between hormone levels and food intake and cravings, H-Group (n = 9) 1 = Withdrawal bleeding, 2 = Active Phase 3 = Active Phase, 4 = Inactive Phase

|	Energy				Carbohydrate				Fat				Protein			
	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
P4	-0.183	0.233	**0.678***	0.083	-0.283	-0.017	0.435	-0.150	0.350	**0.683***	**0.695***	0.067	-0.417	0.133	0.402	0.1
E2	0.017	0.167	**0.767***	0.467	-0.233	0.067	**0.833****	0.4	0.067	0.417	0.317	0.067	0.233	0.2	0.583	**0.667***
L	0.267	0.533	0.183	-0.017	0.133	0.517	0.350	0.05	0.467	0.367	0.167	0.017	-0.033	0.3	-0.250	0.1
GR	-0.350	-0.483	-0.350	-0.233	-0.417	-0.5	-0.283	-0.4	-0.467	-0.333	-0.417	-0.217	0.383	-0.167	0.200	-0.05
I	0.05	0.483	**0.667***	-0.46	0.117	0.550	0.4	0.123	0.367	0.250	**0.683***	-0.186	-0.467	0.450	0.300	-0.421
GL	0.076	0.650	0.4	0.301	0.025	**0.667***	0.183	0.268	0.504	0.285	0.597	0.008	-0.345	**0.883***	0.350	0.510

r = Spearman's correlation coefficient
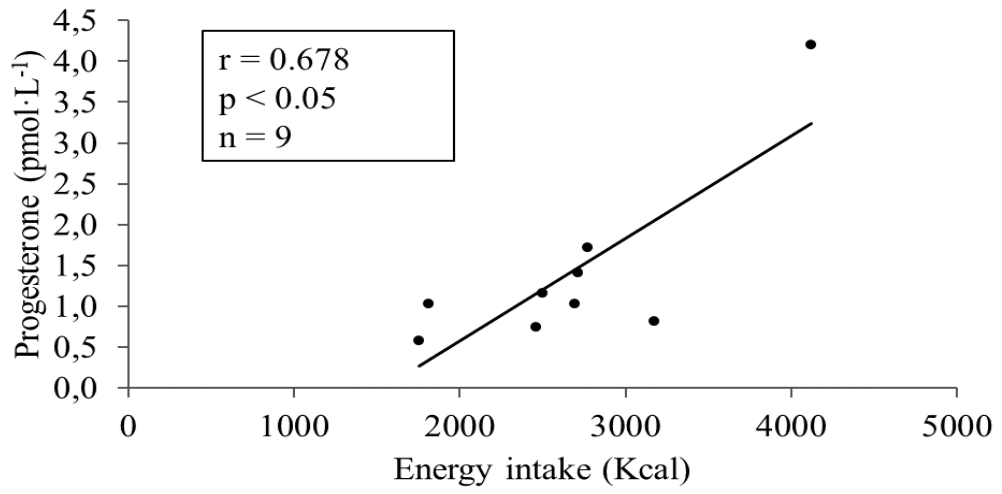
FIGURE 17. The correlation between progesterone and energy intake in the second active phase, H-group

8.4 Associations between sex hormone levels and satiety hormone levels

Correlations between ovarian steroid hormones and leptin, ghrelin, insulin, or glucose were not identified in the N-group (Table 8). Progesterone correlated positively to insulin during the second active phase in the H-group (r=0.703. p<0.05).

TABLE 8. Correlation coefficients (r-values) between estradiol, progesterone and leptin, ghrelin, insulin and fasting glucose, N-group (n = 16) 1 = Menstrual Phase, 2 = Follicular phase, 3 = Ovulation, 4 = Luteal phase

	Leptin				Ghrelin				Insulin				Glucose			
	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
P4	0.462	0.172	0.165	0.270	0.029	0.166	-0.09	0.187	0.4	-0.021	-0.165	-0.161	-0.127	0.215	-0.015	0.439
E2	0.446	0.175	0.231	0.376	0.125	0.036	-0.130	-0.033	0.177	0.112	0.398	0.282	0.211	-0.397	0.145	0.126

r = Spearman's correlation coefficient

TABLE 9. Correlation coefficients (r-values) between estradiol, progesterone and leptin, ghrelin, insulin and fasting glucose, H-group (n = 9) 1 = Withdrawal bleeding, 2 = First Active Phase 3 = Second Active Phase, 4 = Inactive Phase

	Leptin				Ghrelin				Insulin				Glucose			
	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
P4	0.05	0.3	0.268	0.1	-0.517	-0.317	-0.310	0.017	0.550	0.05	**0.703***	0.001	0.597	0.383	0.483	0.268
E2	0.167	0.633	0.35	0.5	-0.2	-0.05	-0.267	-0.250	-0.405	-0.333	0.048	0.095	0.387	0.367	0.317	0.577

r = Spearman's correlation coefficient

9 DISCUSSION

To the best of knowledge, this was the first study to investigate associations between the menstrual cycle, hormonal contraceptive use, dietary intake, and satiety hormones in recreationally active healthy women. The main findings of the present study are as follows:

1) In accordance with the hypothesis, significant elevation in leptin was observed during the ovulation and in the luteal phase compared to the menstrual phase and the follicular phase. No alterations were detected in other satiety hormones, or in fasting glucose between measurement points in either of the groups.

2) Unlike other research carried out in the field, energy intake or macronutrient intake was not found to change across the menstrual cycle or the hormonal contraceptive use. Against the hypothesis, energy intake or cravings did not increase in the luteal phase or decrease at ovulation. Surprisingly, the H-group reported significantly more cravings during the withdrawal bleeding and the first active phase compared to the corresponding phases of the N-group. In addition, some variation was observed in progesterone across cravings in both groups. Those subjects who reported cravings in the follicular phase had higher progesterone compared to those who did not report cravings. In the H-group, similar phenomenon was identified during the withdrawal bleeding. Furthermore, subjects without cravings had higher estradiol in the second active phase.

3) Some positive and negative correlations between the dietary intake and hormones were identified in both groups. Contrary to expectations, ovarian steroid hormones and food intake were not associated in the N-group. Instead, leptin in the luteal phase and insulin at ovulation had inverse relationships with protein intake. In the H-group, progesterone was positively associated with energy and fat intake during the active phase of hormonal contraception.

9.1 Satiety hormones and the menstrual cycle

The most remarkable finding emerging from this study is the variation in leptin during the menstrual cycle, which is in line with previous research. Ajala et al. (2013) suggested that several factors determining leptin expression might have potential to account for varying concentrations across the menstrual cycle phases, including regulatory properties of ovarian steroid hormones. Although some studies have suggested that leptin parallels concentrations of progesterone (Hardie et al. 1997; Paolisso et al. 1999; Ahrens et al. 2013), it was not demonstrated in the present study. Another interesting speculation, provided by Cella et al. (2000), suggests that typical structural and functional events at the time of potential egg implantation might contribute to higher leptin around the ovulation and during the luteal phase. This is further supported by the documented existence of leptin receptors in ovaries, follicles and the corpus luteum (Karlsson et al. 1997; Hausman et al. 2012).

Slight variation in the exact time of the increase in leptin has been observed, since some studies have recorded peak values during the luteal phase (Hardie et al. 1997; Ludwig et al. 2000) and others at ovulation (Hardie et al. 1997; Cella et al. 2000; Ahrens et al. 2014). In the present study, concentrations were at their highest during ovulation. However, not all studies have agreed on this. Teirmaa et al. (1998), Lin (1999) and Stock et al. (1999) reported non-significant variation in leptin across the phases. Major pitfalls limiting the comparability of the data are methodological differences, including variation in blood assays and verification methods of the menstrual cycle. In addition, relatively large interindividual variation reported in previous studies (Thong et al. 2000) was present in the current study as well.

Since fat mass and food intake of subjects remained constant across the period of interest, it can be presumed that the change in leptin was not due to at least dramatic energy imbalances. Hence, it must be explained by other mechanisms, such as above mentioned post-ovulatory changes. This is also substantiated by the finding that similar variation of leptin was not observed in the H-group.

In the present study, the phase effect of the menstrual cycle or hormonal contraceptive use on ghrelin, fasting insulin or fasting glucose was not observed, which is mostly in agreement with existing literature. Only insulin has been shown to vary across the menstrual cycle (Yeung et al. 2010). It is noteworthy to consider that the majority of studies investigating relationship between glucose metabolism and menstrual cycle have tested insulin sensitivity and glucose tolerance, with very few assessing only fasting concentrations.

Although no study to date has demonstrated relationship between ghrelin and menstrual cycle in healthy women, Townsend (2016) has suggested that its existence cannot be completely ruled out, since several studies have demonstrated that exogenous estradiol have influence on ghrelin in rats (Matsubara et al. 2004) and in women suffering from anorexia (Grinspoon et al. 2004) or polycystic ovarian syndrome (Sagsöz et al. 2009). However, oral contraceptives were not capable of influencing ghrelin in healthy women (Dafopoulos 2010), which is in good agreement with the results of this study. Furthermore, it is essential to consider methodological discrepancies between studies, as some have assessed UnAG and AG separately (Dafopoulos et al. 2010) and some solely AG (Townsend 2016). As previously stated, AG seems to have greater significance in regards of appetite stimulation, while total ghrelin reflects mainly the UnAG, representing as much as 90 % of total plasma concentration (Cappellari & Barazzoni 2018). In this study, the total ghrelin was assessed, thus results cannot be directly compared with previous findings.

9.2 Ovarian steroid hormones in relationship with dietary intake

In this study, dietary intake did not vary across either the menstrual cycle or hormonal contraceptive use. The H-group had overall higher energy intake in relation to body mass in comparison with the N-group, which may be simply explained by the differences in daily caloric requirements. Furthermore, correlations were identified between some hormones and dietary variables in the H-group, but no systematic trend was found. As previously emphasized, a convincing amount of evidence indicates that energy intake fluctuates across the menstrual cycle. Thus, results of this study can be regarded somewhat unusual.

There are several factors accounting for the discrepancy between this study and previous literature. As is well known, the field of food intake research is sensitive to a numerous of confounding factors, such as personality traits (Kipnis et al. 2003) and psychological aspects (Asbeck et al. 2002). In the present study, inclusion criteria required subjects to be recreationally active women, but competitive athletes were not excluded from the study. Careful attention must be paid when assessing food intake of athletes due to the special issues related to portion sizes, snacking and seasonality of activities (Magkos & Yannakoulia 2003) as well as the increased risk of disordered eating (De Oliveira Coelho et al. 2014). It is common for athletes to follow a specific diet to maximize the performance (Maughan 2007) and nutritional strategies may be altered only consciously, for instance when training volume or intensity changes remarkably. Perhaps the sample of athletic women might not be the most optimal to

represent intuitive eating, considering that biological needs may be overridden by cognitive restraint (Buffenstein et al. 1995; Li et al. 1999). Furthermore, there is a quite fine line between the disordered eating and strict dietary regimens. Although all subjects enrolling in the present study were healthy according the LEAF-Q and the health questionnaire, history of disordered eating was not screened prior to study entry. Thus, it cannot be excluded that subtle problematic eating behavior might have been present in some of the subjects, possibly obscuring the real associations between the menstrual cycle and energy intake.

The current study observed moderate positive relationships between progesterone and energy intake, as well as between progesterone and fat intake during the active phase of hormonal contraception. Previous research does not provide definitive evidence on the relationship between hormonal contraception and food intake. In terms of well-defined appetite stimulating nature of progesterone, some speculations can be made. Hirschberg (2012) suggested that androgenicity of specific progestin contained in the contraceptive might account for fluctuations in appetite, which is further supported by studies demonstrating that androgenic progestins have shown to restore appetite in undernourished patients (Maltoni et al. 2001; Vanhoutte et al. 2016). In addition, there is some evidence substantiating the suppressive effects of androgenic oral contraceptives on appetite inhibiting CCK (Hirschberg et al. 1996). However, in the present study, the majority of subjects in the H-group used combined pill that contained highly antiandrogenic drospirenone (Regidor & Schindler 2017), which has been suggested to attenuate binge eating, at least in bulimic women (Naessén et al. 2007). Interestingly, also estradiol correlated positively with energy intake and carbohydrate intake during the active phase of the contraception in the present study. To conclude, it is challenging to interpret these inconsistencies due to a paucity of studies investigating associations between hormonal contraception and food intake, and undefined mechanism behind their potential appetite stimulating effects.

9.3 Ovarian steroid hormones in relationship with cravings

Results of this study demonstrated between-group differences in cravings, as well as variation in ovarian steroid hormone levels across reported cravings in both groups, which at least hints that some associations may exist. However, findings must be interpreted with caution, given the inconsistent patterns they exhibited.

A limited number of prior studies have not observed any differences in cravings between hormonal contraceptive users and naturally cycling women (Bancroft & Rennie 1993; Tucci et

al. 2010), so it is certainly difficult to explain why the H-group reported more cravings compared to the N-group during the first half of the cycle. Most subjects in the H-group used monophasic oral contraceptive preparation that provides equal amount of synthetic progestin and estradiol during the active phase of the pill, which leads to the presumption that observed between-group differences most likely do not stem from fluctuating ovarian steroid hormone levels.

There is a lack of consensus in previous research evaluating the relationship between progesterone and cravings in naturally cycling women as well. It has been suggested that higher frequency of cravings during the luteal phase is related to the orexigenic effects of progesterone (Dye & Blundell 1997; Hirschberg 2012). In contrast, some studies have proposed, although without direct evidence, that the premenstrual low progesterone may predict cravings (Michener et al. 1999), given that they appear to be linked to the premenstrual syndrome (York et al. 1989). Nevertheless, premenstrual symptoms were not evaluated in the present study, and the subjects who reported cravings possessed higher progesterone compared to the subjects without cravings in the follicular phase, when progesterone levels were at their nadir and equal to those of the H-group. Regarding the evidence of estradiol as appetite suppressant in humans (Asarian & Geary 2006), it is interesting finding that those subjects who did not report cravings in the second active phase had higher estradiol. However, large interindividual variation and one subject with abnormally high level of estradiol in the H-group may be more appropriate explanation rather than anorexigenic effects of estradiol. It is crucial to note that the concept of cravings comprises a sum of complex factors including social and psychological dimensions along with hormones, thus these findings do not allow strong conclusions.

9.4 Associations between satiety hormones and dietary intake

Both leptin and insulin were found to correlate negatively with protein intake during the latter half of the menstrual cycle. This is an interesting finding since leptin and insulin has been shown to activate same anorexigenic hypothalamic neurons (Schwartz et al. 1991; Benoit et al. 2002). However, the significance of this finding remains to be determined.

Hypothesized associations between leptin, ghrelin and energy intake were not present in this study. For leptin, this result agrees with the hypothesis based on recent studies focusing on these factors in women but contradicts with the well-documented anorexigenic effects of leptin. A question of interest is whether the previously documented inverse associations between leptin and food intake are compromised during the menstrual cycle. The results of present study

concur well with previous studies (Paolisso et al. 1999, Gil et al. 2009, Chung et al. 2010), where the association between leptin and food intake was not identified across the menstrual cycle. Paolisso et al. (1999) hypothesized that a slight increase in leptin across the menstrual cycle might not be enough to induce a remarkable change in food intake. In contrast, Krishnan et al. (2016) found the significant correlation between leptin and reduced sweet food intake but failed to confirm the typical elevation of leptin towards the latter half of the menstrual cycle. They speculated that differences in sweet food intake and cravings may reflect interindividual variation in hormonal ratios instead of only leptin. Another intriguing hypothesis, suggested by Thong et al. (2000), is that the luteal phase increase in leptin may result from temporary leptin resistance and a subsequent decrease in leptin sensitivity. This presumptive mechanism would also explain the controversy between generally observed higher energy consumption during the luteal phase, regardless of higher leptin. However, further experimental evidence is warranted to confirm these highly speculative suggestions.

9.5 Methodological limitations and strengths

A number of limitations need to be considered regarding the present study. First, one of the most important pitfalls lies in the incapacity to control for underreporting, which has been proposed to be the fundamental methodological disadvantage of all dietary assessment methods (Macdiarmid & Blundell 1998). Scagliusi et al. (2003) have shown that as much as 49% of women underreported their energy intake by 21 %. Meta-analysis conducted by Capling et al. (2017) suggests that athletes tend to underestimate their energy intake by 19%. Second, the dietary intake was assessed in total of 12 days. Previous research has indicated that recording over 10 days may lead to problems with motivation and compliance (Ortega et al. 2015). In addition, recording days depended on the testing day, thus some of the subjects did not fill the diary on the weekend days. This is a significant drawback since energy intake has been suggested to be higher on weekends (Monteiro et al. 2017).

Third, the cross-sectional design of this study is a major barrier for identifying the causality of observed relationships between hormones and dietary intake. It would be interesting to further monitor whether leptin and insulin have systematically negative relationship with protein intake in the second half of the menstrual cycle, given that previous studies have shown that dietary proteins are instead positively correlated with insulin, and thereby associated with an increased risk of type 2 diabetes (Rietman et al. 2014). Furthermore, following the subjects for only one cycle may be insufficient timespan to truly capture the natural intraindividual variation in food

consumption. Finally, sample size was relatively small, leading to low statistical power and reproducibility of findings.

Despite the above-mentioned shortcomings, the present study has several strengths. First, the study methodology adopted the current best practices in the field of menstrual cycle and nutrition research (Ortega et al. 2015; De Jonge et al. 2019). The dietary intake was assessed with food records over a sufficient length of time and the menstrual cycle phases were determined by the combination of ovulation detection by urine LH-surge and counting method. Subjects were measured four times throughout the cycle, and hormonal data indicate correct verification of the menstrual cycle phases. Furthermore, the compliance of subjects was acceptable in terms of both food record submission and relatively low drop-out rate.

9.6 Conclusions

The main objective of the current study was to determine whether satiety hormones or ovarian steroid hormones might play role in modifications of dietary intake in recreationally active premenopausal women. Returning to hypothesis, results do not offer compelling evidence for the alterations of dietary intake in women using or not using hormonal contraceptives. Progesterone, whether exogenous or endogenous, irrespective of cycle phase, may be related to increased cravings. Therefore, this study suggests that athletic women battling against the constantly fluctuating ovarian steroid hormones may not be more vulnerable to experience challenges in their habitual eating behavior or the maintenance of body weight compared to their counterparts using hormonal contraception with more stable hormonal milieu. However, inconsistency in associations between hormones and dietary intake reflects not only methodological challenges but also the complexity of female endocrinology and appetite. Finally, this study succeeded to confirm previously demonstrated variance in leptin during the menstrual cycle, which extends the understanding of physiological significance of leptin as an indicator of optimal health, including energy availability and eumenorrhea. Future studies should aim to replicate the study design with larger sample size, and in non-athletic populations.

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