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REVIEW

Variation of Leptin During Menstrual Cycle and Its Relation to the Hypothalamic–Pituitary–Gonadal (HPG) Axis: A Systematic Review

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Abstract: Recently, adipose tissue has been identified as endocrine organ in addition to its action as energy store; it produces a large number of biologically active mediators known as adipocytokines. Significantly, adipocytokines were found to be involved in the physiology of many body functions, including reproduction. The role of body weight, body fat compositions, and nutrition has been largely investigated using animal models and human studies. Malnutrition and/or abnormal body weight may induce disturbances in fertility, puberty, pregnancy, and menstrual cycles. Leptin was the first discovered adipocytokine, and a large body of data over the last 25 years has shown that leptin is not only a molecule that reflects energy stores in the body, but is also an important cytokine involved in many physiological functions, such as inflammatory response, insulin sensitivity, bone metabolism, immunity, and most importantly, reproductive function. Leptin controls the normal physiology of the female reproductive system; it interacts with the hypothalamic–pituitary–gonadal (HPG) axis by a complex mechanism that connects energy homeostasis with reproduction. However, observational studies have demonstrated inconsistent results about leptin variation during normal menstrual cycle, and the mechanisms involved in the interplay between leptin and the hormones of the HPG axis are largely unknown. This review focuses on leptin variation during normal menstrual cycles and its relation to the hypothalamic–pituitary–gonadal axis, and the effect of overweight/obesity on leptin during menstrual cycle is further reviewed.

Keywords: leptin, adipocytokines, menstrual cycle, sex hormones, obesity

Introduction

The physiology of energy homeostasis and the control of appetite have greatly changed since the discovery of leptin, an adipose tissue hormone that was first purified in 1995.[1] Recently, a wide range of physiological functions of leptin have been described, and leptin was found to exert a regulatory control upon insulin sensitivity, immune function, reproductive function and a wide range of neuroendocrine axes: ACTH-cortisol, TRH-TSH, prolactin, and GnRH. Leptin signals about the body-fat stores to the hypothalamus and other neuroendocrine centers, and as a feedback response, the neuroendocrine systems modify their function accordingly.[2,3]

Many reviews described the role of leptin in human reproduction comprehensively, showing a key role of leptin in the complex interaction between the nutritional status and the reproductive system.[4,5] The association between leptin and reproduction was first described by observing that *ob/ob* gene deficient female mice were obese and sterile.[6] Humans with congenital leptin deficiency also have obesity and infertilely and

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showed failure in puberty development due to hypogonadotropic hypogonadism.[7] Both obesity and undernutrition were found to affect fertility in humans.[8,9] Furthermore, leptin play a permissive action for puberty both in girls and boys with obesity, specifically by affecting the hypothalamic–pituitary–gonadal axis.[10]

Leptin has a role in the physiology of female reproduction in particular, as it showed gender-related differences at birth, which persist throughout life with a circulating level two to three times higher in females than in males.[5] Serum leptin in women with hypothalamic amenorrhea was lower than in healthy control women, and administration of leptin restored the menstrual cycles and fertility.[11] Recently, several studies showed the involvement of leptin in the development of several pregnancy-related diseases such as gestational diabetes.[12–14] All these findings led to the development of the hypothesis for leptin as an important player in the female reproduction system via its stimulatory effect on the hypothalamic–pituitary–gonadal axis.[3,15]

The role of leptin in the menstrual cycle and female reproduction was first suggested in the late 1990s; several studies noticed a significant variation in serum leptin during the female menstrual cycle,[16–20] but this variation was absent in postmenopausal women.[20] Subsequently, many studies showed inconsistent leptin behavior throughout the menstrual cycle, and some reported steady increments in leptin levels from the follicular phase to reach a peak in luteal phase,[21–24] and others showed a peak during the preovulatory phase[25] while a stable level of leptin across menstruation was also described.[26–28] However, this discrepancy highlights a certain role of leptin signaling during the menstrual cycle, but the mechanism of this role is still to be explored.

Currently, there is no review that explores specifically the variation of leptin during the menstrual cycle and its relation to the hypothalamic–pituitary–gonadal axis. In addition, the effect of body weight on leptin during menstrual cycle is not fully elucidated. Thus, the aim of this review is to examine the variation of leptin during the menstrual cycles and its relation to the hypothalamic–pituitary–gonadal axis and to body weight. This review was carried out according to the guidlines provided by the Preferred Reporting Items of Systematic Reviews and Meta-analyses (PRISMA) statement.[29]

Methods

Information Sources and Search Strategy

Medline/PubMed and Google Scholar databases were searched for studies of leptin during normal menstrual cycle since 1995 (the time of leptin discovery) until October 2020. The search strategy used keywords related to leptin and menstrual cycle (adipokines[Title] OR adipocytokines[Title]) OR adipose tissue hormones[Title]) OR leptin[Title]) AND menstrual cycle[Title/Abstract]) OR Endometrial Cycle[Title/Abstract]) OR ovarian cycle[Title/Abstract]) AND "humans"[MeSH Terms]). Further searching through ISI and Scopus and by manual screening the bibliographic references of the selected studies did not yield any additional papers. No language restriction was applied, and the retrieved references were imported into EndNote X5.

Study Selection

The titles were screened for relevance to the aims and scope of the current review; those studies falling within the scope and were further screened by abstract to determine the eligibility according to inclusion and exclusion criteria. The following inclusion criteria were applied: (a) prospective observational studies that had been run over one or more complete normal menstrual cycles; (b) the study population were adult healthy women with regular menstrual cycles; (c) the primary outcome of the studies was the variation of leptin levels during different phases of the menstrual cycle, with or without investigation of the relationship between leptin and the body weight (BMI); (d) leptin and other hormones assays were conducted in blood or saliva samples during different phases of the menstrual cycle. The current review excluded: (a) studies evaluating irregular menstrual cycles; (b) menstrual cycle in females with associated gynecological diseases or comorbidities, eg, polycystic ovary syndrome (PCOS); (c) studies with less than one complete cycle duration; and (d) randomized clinical studies RCT, review, systematic review, meta-analysis, case report, comments, editorials, letters and animal studies. After the preliminary eligibility screening evaluation, the full articles of the selected studies were obtained (Figure 1).

The following data were extracted from the selected studies:

- General information about the study: author(s), journal name, title, publication year, study design, and location of the study
- Age of the subjects
- Number of participants
- Duration of the study (number of cycles evaluated)
- Frequency of leptin sampling during each cycle
- Major outcomes and conclusion
- Limitations if any

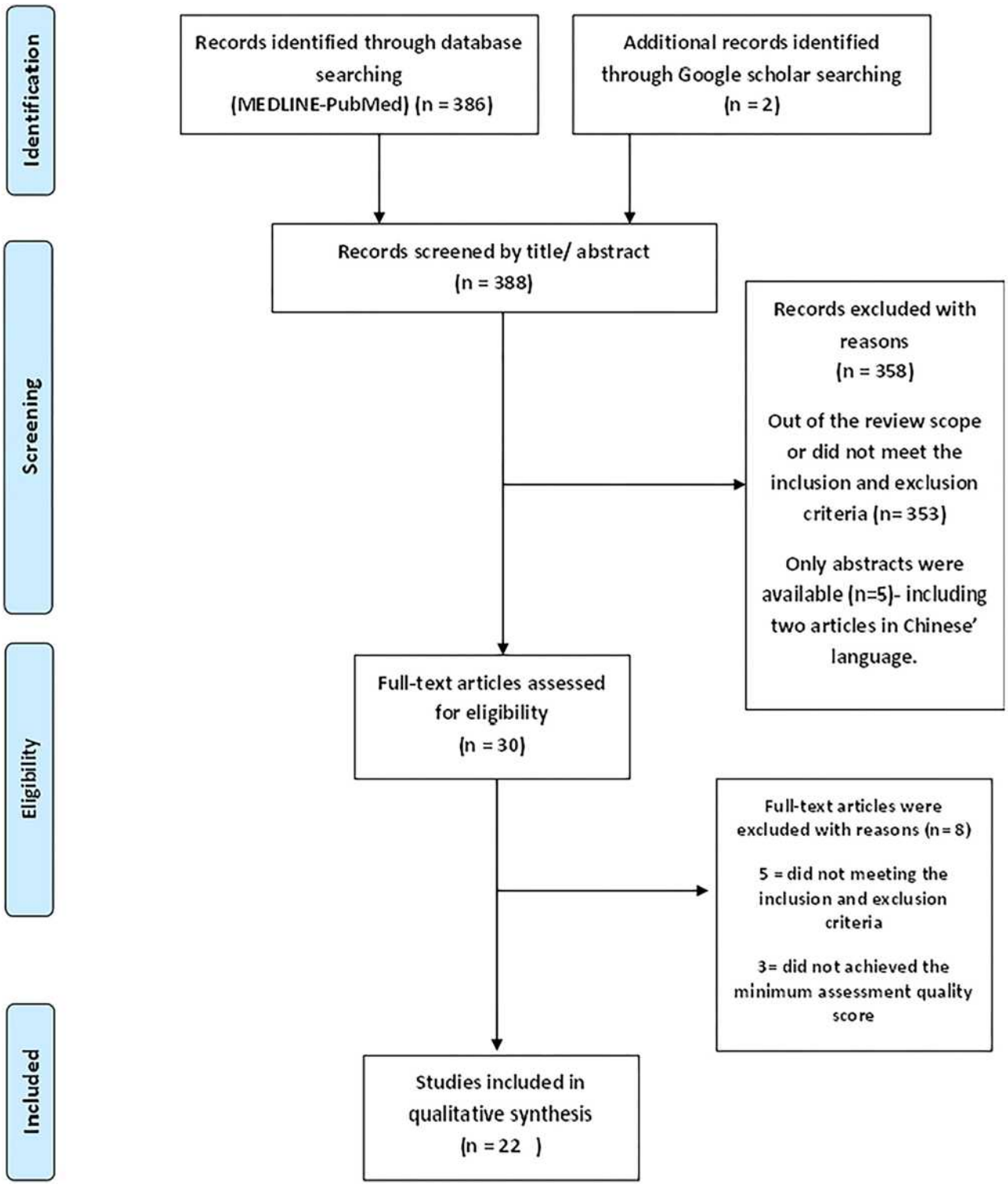

Figure 1 Flow chart of the literature search and selection process.

Quality Assessment

Based on a six-point scale by Hayden et al[30] the following criteria was used to evaluate the quality of each selected study: (1) study participation (the sample is large enough and represents the population of interest); (2) study attrition (full explanation of the sample drop out); (3) determination of the factor of interest (clear definition and description of the factor of interest is provided); (4)

confounding factors control; (5) outcome measurement (full explanation of the method used for outcome measurement in such a way that reduces measurement bias; and (6) appropriateness of statistical analysis. One point score was given for each criterion; the score of 0–3 points indicated low quality studies, while scores above 3–6 were considered high-quality studies.

Results

A primary search by MEDLINE/PubMed identified 388 articles; two extra articles were identified by Google Scholar search. By screening the titles and the abstracts, 358 articles were excluded for reasons of scope and/or not meeting the inclusion and exclusion criteria of the review. A total of 30 full-text articles were retrieved and analyzed for eligibility; of these, eight articles were excluded because five of them did not meet the inclusion and exclusion criteria and three articles did not achieve a minimum quality assessment score (≤3). Finally, 22 articles were included for the qualitative analysis in the current review (Figure 1).

The selected studies included women from 14 countries: Poland,[31] Czech Republic,[28] Germany,[16,32–34] Saudi Arabia,[35,36] USA,[20,37] Greece,[24] Switzerland,[23] Spain,[38] Italy,[18,27,39,40] Austria,[41] UK,[17] Japan,[42] Sweden,[43] and Finland.[44] These studies included cycling women with a wide age range (18–44 years), and the number of cases ranged from six[17] to 259[37] women. All studies were prospective observational studies, except four clinical studies that included multiple groups.[16,39,43,44] In these four studies, leptin variation during menstrual cycle was determined on the control groups, which included spontaneous cycling women without any intervention; thus, they have been included in the present review. The majority of the studies had evaluated leptin during one complete menstrual cycle; however, two studies had evaluated leptin over three consecutive menstrual cycles[16,32] and one study over two consecutive menstrual cycles.[37] All studies measured leptin in the blood, except one study that evaluated leptin variation during menstrual cycle in a saliva sample.[33]

Variation of Leptin During Menstrual Cycle

Of the included studies, 18 have shown significant changes in leptin level across different phases of the menstrual cycle[16–20,23,24,31–39,41,43] (Table 1), while four studies reported no changes in leptin throughout the menstrual cycle[27,28,42,44] (Table 2). Most of the studies reported significant changes in leptin and showed a steady increment from the lowest level at the early follicular phase to its peak at late luteal phase—except two studies, where leptin peak was detected at the mid-cycle phase near the time of LH surge.[37,39]

Relationship Between Leptin Variation During Menstrual Cycle and the Hypothalamic–Pituitary–Gonadal Hormones

The relationship of leptin during menstrual cycle with at least one of the hormones of the hypothalamic–pituitary–gonadal axis was evaluated by 17 studies,[17–20,23,24,27,31,33–39,42,44] as seen in Tables 1–2.

Effect of Obesity on Leptin Variation During Menstrual Cycle

Among the selected studies, only four studies investigated the effect of obesity on leptin variation during menstrual cycle by comparing normal weight women with overweight/obese women.[35,36,38,42] Two studies showed significant fluctuation of leptin level with the lowest values during the early follicular phase and the highest during the luteal phase in both normal weight and overweight/obese groups.[35,36] In contrast, one study detected leptin variation during the menstrual cycle in the normal group with higher levels during preovulatory and luteal phase, while overweight women showed stable leptin level.[38] Another study reported no changes in leptin levels during the menstrual cycle in the normal weight group, while leptin showed significant variation during the luteal phase in the obese group.[42]

Discussion

The role of leptin in the reproductive function in humans is well documented. Leptin is considered to be the link between body fat storage and the hypothalamic–pituitary–gonadal axis. Many human and animal studies suggest that leptin has also been implicated in the physiology of puberty, menstrual cycle, menopause, pregnancy, and lactation.[45] However, the role of leptin during the menstrual cycle showed some controversy. In addition, the mechanism describes the effect of obesity on leptin level during the menstrual cycle needs further review and analysis.

Table 1 Summary of 18 Studies That Showed Significant Variation of Leptin During Different Phases of the Menstrual Cycle

Studies	Location	Mean Age	Subjects Studied	Study Design	Duration	Frequency of Sampling	Main Conclusion	Limitation	Quality Score
Ahrens et al (2014)—The Bio Cycle Study (2005–2007)[37]	USA	27±8.2 years	259 healthy premenopausal women with regular menstruation BMI=18–35	Prospective cohort study	One cycle (n=9) two cycles (n=250)	Eight samples per cycle during the following phases: menses, early and late follicular phase, LH surge, ovulation, early, mid, and late luteal phases	Serum leptin increased from menstruation to the late luteal phase with a mid-cycle peak. Leptin was positively correlated with estradiol, progesterone, testosterone, LH, and negatively with FSH	Involved women of BMI between 18 and 35 which limits the generalization of the findings due to leptin insensitivity that develops in obese subjects	6
Geisthovel et al (2004)[32]	Germany	29±4.25 years	30 regular menstruating women (BMI=20 ±1.3),	Prospective observational study	Three consecutive menstrual cycles	Measurement were performed twice throughout all phases of the menstrual cycle II (early and mid-follicular phase, preovulatory phase and early and late luteal phase), additional two measurements were done on cycle III during early and mid-follicular phase, preovulatory phase	Significant variation of leptin was observed with a steady increment from early follicular phase to reaches its peak at late luteal phase	Small sample size	5
Riad-Gabrirel et al (1998)[20]	USA	28±2 years	Nine regular menstruating women (BMI=23.9 ±1.8)	Prospective observational study	One complete cycle	Every 1–2 days throughout the menstrual cycle	Leptin concentration was significantly higher during mid-luteal phase compared to follicular phase. No correlations between leptin with estrogen, progesterone, LH, and FSH were detected	Small sample size	5

(*Continued*)

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Table 1 (Continued).

Studies	Location	Mean Age	Subjects Studied	Study Design	Duration	Frequency of Sampling	Main Conclusion	Limitation	Quality Score
Cella et al (2000)[39]	Italy	29.7±4.8 years	Eight women with normal cycle (BMI=22±1.3)	Clinical longitudinal study	One complete cycle	Daily during complete cycle	Leptin varied significantly with higher level during luteal phase compared to follicular phase, with a transient peak in the late follicular phase. Leptin was positively correlated with estradiol and progesterone. No correlation with LH and FSH	Small sample size	5
Wyskida et al (2017)[31]	Poland	18–30 years	52 healthy women with normal menstrual cycle BMI (18-5-24)	Prospective observational study	One menstrual cycle	Three samples between days 2 and 4, 12 and 14, and 24 and 26 of each subject's menstrual cycle	Leptin was significantly higher in both mid-cycle and luteal phase. Leptin significantly related to total testosterone	Less frequent sampling. Determination of menstrual phases based on menstrual rhythm only	4.5
Fernández-Real et al (2000)[38]	Spain	Lean women =35.8 2±2 years Overweight women=37.7 2.1 years	Nineteen normal menstruating women divided into two groups: nine lean women (BMI <25) and 10 overweight women (BMI >25)	Comparative prospective study	One complete cycle	Three times; early follicular (3–4 days from menstruation), mid-cycle (days 12–15) and mid-luteal (days 17–22)	Leptin changed significantly in lean women with higher levels during preovulatory and luteal phase, while overweight women showed stable unaltered leptin level. Leptin were correlated to LH but not with estrogen nor with progesterone	Small sample size less frequent sampling. Determination of phases based on menstrual rhythm only	4.5

Rafique et al, (2018)[36]	Saudi Arabia	19–25 years	Fifty-six females with normal menstrual cycel divided into two groups: 26 normal weight (BMI=18.5–24.99) and 30 overweight/ obese (BMI ≥25)	Comparative prospective study	One complete cycle	Three times: follicular phase (2–3 days from the onset of menstruation), preovulatory (11–16 days before the onset of the next menstrual cycle) and luteal phase (3–5 days before the onset of the next cycle)	Leptin was significantly increase during luteal phase compared to follicular phase in normal weight group. However, in overweight obese group, leptin was significantly higher during both preovulatory and luteal phase compared to follicular phase. No association between leptin with serum estradiol was detected in both groups	Less frequent sampling. Determination of menstrual phases based on menstrual rhythm only	4.5
Ludwig et al (2000)[34]	Germany	Not mentioned	Sixteen normal menstruating women (BMI 18–25)	Prospective observational study	One cycle	Each alternate day during complete cycle starting after day 3 of menstrual cycle.	Leptin showed higher level during luteal phase compared to the follicular phase. No correlation with estrogen and progesterone	Small sample size. Determination of phases based on menstrual rhythm only	4.5
Stock et al (1999)[43]	Sweden	30±5 years	Thirteen women (BMI=22.2±2.5	Prospective observational study	One complete cycle	Four times during menstrual cycle: days 1–3, 6–8,13–15 and 22–25	Small overall significant variation during the menstrual cycle,	Small sample size. Less frequent sampling	4.5
Wunder et al (2006)[23]	Switzerland	25.5±5.5 20–32 years	36 healthy women with normal BMI (18.5–25)	Prospective observational study	One full cycle	Every 1–2 during one complete cycle (14–19 samples per participant)	Leptin was significantly higher during the mid-luteal phase compared to early follicular and ovulatory phases. Leptin was positively correlated with prolactin and testosterone, no correlations with progesterone and estrogen were detected	Small sample size	4.5

(*Continued*)

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Table 1 (Continued).

Studies	Location	Mean Age	Subjects Studied	Study Design	Duration	Frequency of Sampling	Main Conclusion	Limitation	Quality Score
Geisthovel et al (1998)[16]	Germany	22–38 years	Nineteen normal weight women (BMI:18–24)	Clinical study with control group of 19 regularly menstruating women	Three menstrual cycles	Five samples, mid-follicular phase around days 7–9, preovulatory phase, twice during mid-luteal phase (4 days and 6 days after ovulation), and on the mid-follicular phase of the next cycle	Significant cyclic changes were observed with high concentration at preovulatory and mid-luteal phases compared with the two mid-follicular phases	Small sample size	4.5
Al-Harithy et al (2006)[35]	Saudi Arabia	19–39 years	Sixty-five regular menstruating women divided into two groups: 32 normal weight (BMI <25), and 33 overweight/ obese group (BMI >25)	Comparative prospective study	One menstrual cycle	Four samples on day 3, 10, 17 and 24 from the beginning of the menstruation	Leptin varied significantly with lower level during the early follicular phase and the highest during the luteal phase in the two groups. Leptin was significantly correlated with estrogen in both group, and with progesterone in normal weight group, no correlation with testosterone, FSH and LH was found in both groups	Less frequent sampling. Determination of phases based on menstrual rhythm only	4
Asimakopoulos et al (2009)[24]	Greece	19–30 years	Sixteen regular menstruating women (BMI=19.46–24.90)	Prospective observational study	One menstrual cycle	Every alternate day throughout the cycle	Leptin varied significantly with higher values during the luteal phase and mid-cycle phases compared to the follicular phase. Leptin was positively correlated to estrogen, progesterone and negatively with FSH	Small sample size	4

Hardie et al (1997)[17]	UK	31.5±3 years	Six healthy normal menstruating women (BMI=21.6 ± 0.5)	Longitudinal observational study	One complete cycle	Serial sampling start from one day after menstruation then every third day, apart from days 11–17 during which daily sampling was done.	Leptin was significantly higher during periovulatory and luteal phases compared to follicular phase. Leptin was correlated with the progesterone level during luteal phase.	Small sample size	4
Faustman et al (2016)[41]	Austria	34.2±6.5 years	Twenty-eight women, BMI 22.4 ±3.44	Prospective longitudinal study	One complete cycle	Four times early (T1) and late (T2) follicular phase, mid (T3) and late (T4) luteal phase	Leptin was higher during mid-luteal phase compared to the early follicular phase. Progesterone was inversely related to leptin during late follicular and early luteal phase	Small sample size. Determination of phases based only on menstrual rhythm and body basal temperature changes	3.5
Mannucci et al (1998)[18]	Italy	18–35 years	Eighteen normal menstruating women (BMI <27)	Prospective observational study	One full cycle	Four times during the menstrual cycle (day 3,10,17, and 24 from the beginning of menstruation)	Leptin during day 10, 17, and 24 was higher compared to day 3 of the menstrual cycle. No correlation with estradiol, progesterone, testosterone, DHEAS, androstenedione, LH, and FSH	Small sample size and less frequent sampling. Determination of phases based on menstrual rhythm only	3.5
Paolisso et al (1999)[19]	Italy	26.1±0.8 years	Sixteen women with normal menstrual cycle (BMI=21.1±0.3)	Prospective observational study	One complete cycle	Three times: follicular phase (days 4–7), periovulatory phase (day of luteinizing hormone (LH) surge ±1 day], luteal phase (days 23–27).	Leptin was significantly changed during menstrual cycle. A positive correlation between leptin concentration and progesterone level was detected throughout all menstrual phases.	Small sample size and less frequent sampling	3.5

(*Continued*)

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Table 1 (Continued).

Studies	Location	Mean Age	Subjects Studied	Study Design	Duration	Frequency of Sampling	Main Conclusion	Limitation	Quality Score
Gröschl et al (2002)[33]	Germany	19–22 years	Ten healthy normal women with normal menstrual cycle (BMI=19.5–22.2)	Observational prospective study	One complete cycle	Daily during one complete menstrual cycle	Salivary leptin showed significantly higher level during luteal phase compared to follicular phase. Leptin was positively correlated with progesterone	Small sample size. Determination of phases based on menstrual rhythm only	3.5

The majority of the studies evaluating leptin in normal-weight, regularly menstruating females showed a significant variation during the menstrual cycle (Table 1). Only a few studies reported a small nonsignificant variation in leptin level across menstruation[27,28,42,44] (Table 2). This insignificant variation could be attributed to the small sample size and method of determination of the menstrual phases in these studies, which is based on menstrual rhythm only. However, some of these studies reported a significant variation in leptin during the menstrual cycle in the obese group,[42] while others showed high leptin levels in the ovulatory cycle group compared to the nonovulatory cycle[27] and a positive correlation with LH level.[44]

The pattern of leptin variation during menstrual cycle is almost similar among all studies; leptin showed a high concentration during preovulatory and luteal phases when compared to the follicular phase with a steady increment starting from the follicular phase through the ovulatory phase and reaching a peak during the luteal phase (Table 1). However, two studies detected a peak of leptin just before ovulation, which coincides with LH surge (preovulatory peak),[25,39] but this peak was not significantly different from the high luteal leptin level reported by these studies.

To control for the effect of adiposity on leptin variation during menstrual cycle, only normal weight women with BMI <25 were included in most of the studies. However, some studies had further demonstrated significant leptin variation during the menstrual cycle in overweight/obese women similar to the pattern observed in normal weight women.[35,36,42] The presence of leptin variation in obese women indicates factors other than adiposity are implicated in leptin variation during menstruation. Corpus luteum formation during the luteinization phase could be possible cause of elevated leptin, and corpus luteum has been found to produce leptin in human[46] and bovine models.[47] Further support came from comparing ovulatory and anovulatory cycles; decreased leptin concentration was found during the anovulatory cycle (ie, without ovulation and corpus luteum) compared to the corresponding higher leptin level during the luteal phase of the ovulatory cycles (with ovulation and corpus luteum formation).[25,27] In addition, the LH surge during ovulation stimulates the production of many inflammatory mediators within the ovarian follicles.[48] Because leptin is considered a pro-inflammatory mediator,[49] the high serum leptin during

Table 2 Summary of Four Studies That Showed Stable Leptin Level During Different Phases of the Menstrual Cycle

Studies	Location	Mean Age	Subjects Studied	Study Design	Duration	Frequency of Sampling	Main Conclusion	Limitation	Quality Score
Šrámková et al (2015)[28]	Czech republic	31.8 ±3.56 years	Twenty-seven women with normal menstrual cycle (BMI 22.9±2.8)	Prospective observational study	One full cycle	Every three days for a total of 10 samples starting from the first or second day after menstruation	Leptin showed nonsignificant increase during ovulation	Small sample size. Determination of the menstrual phases based on menstrual rhythm only	3
Capobianco et al (2010)[27]	Italy	21–44 years	Eighteen normal menstruating women (BMI=18.4–25.4) divided into two groups. Ovulatory (N=10) and anovulatory group (N=8)	Prospective observational study	One full cycle	Three times: at menstrual phase (days 2–3), preovulatory (days 12–13), and luteal phase (days 23–24)	No significant change in leptin in both ovulatory and nonovulatory cycles. Leptin was significantly higher in ovulatory group compared to nonovulatory cycle. Leptin was positively correlated with FSH, no associations with estrogen, progesterone, and LH	Small sample size less frequent sampling. Determination of phases based on menstrual rhythm only	4.5
Maruyama et al (2001)[42]	Japan	Normal weight (35.1±4 years) obese (34.2± 2 years)	Ten healthy women divided into two groups: 5 normal weight group (n=5, BMI=22.4±0.3) obese group (n=5, BMI=28.2 ±0.9)	Comparative prospective study	One full cycle	Three blood samples, early follicular (between days 2 and 5 after the onset of menses, ovulatory phase (first and third day after LH surge, and luteal phase (seventh day after LH surge	Normal group showed no change in serum leptin, Leptin was significantly higher during luteal phase in obese group, leptin was significantly correlated with estrogen both in normal weight and obese groups,	Small sample size less frequent sampling	4
Teirmaa et al (1998)[44]	Finland	23.5 ±2.1 years	Eight women with normal menstrual cycle (BMI 21.2±1.6)	Prospective observational study	One full cycle	Three blood samples: between the second and fifth days, the 14th or 15th day, and between the 24th and 26th days of the cycle	There was no significant change in leptin during the different phase of menstrual cycle. Leptin was positively correlate with LH but not with estrogen and progesterone.	Small sample size less frequent sampling. Determination of phases based on menstrual rhythm only	3.5

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preovulatory and the luteal phases might be related to inflammatory responses associated with ovulation.

Leptin produces a regulatory role on the menstrual cycle exerted at the hypothalamic–pituitary–gonadal axis both directly and indirectly.[50] Since the GnRH neurons have no leptin receptors, the action of leptin on the hypothalamic–pituitary–gonadal axis was found to be mediated through intermediate neurons.[45] Intermediate neurons connected to the GnRH neurons on the hypothalamus and control the GnRH secretion through release of neuropeptides, such as proopiomelanocortin (POMC), neuropeptide Y (NPY), and kisspeptin.[5,50,51] In addition, leptin could induce LH secretion directly from anterior pituitary.[52,53] As further proof for the permissive action of leptin on the menstrual cycle, menstruation was restored by administration of recombinant leptin in females with hypothalamic amenorrhea.[11,54]

The literature on the relationship between leptin and female sex hormones during the menstrual cycle is inconsistent. Leptin was found to be positively correlated with estrogen and progesterone during the menstrual cycle in many studies.[17,19,24,33,35,37,39] In contrast, other studies reported no relationship of leptin levels with sex hormones during different menstrual phases.[18,20,23,34,36,38] However, the absence of correlation between leptin and sex hormones reported by some studies does not mean an absence of leptin's role during the menstrual cycle. These controversial results might highlight a complex feedback loop controlling the interrelation between leptin and the hormones of hypothalamic–pituitary–gonadal axis, instead of a simple unidirectional relation.

Conclusion

This review clearly reports a significant variation of leptin hormone across the menstrual cycle, with a significant interplay with other hypothalamic–pituitary–gonadal hormones. Further studies on the molecular mechanism of leptin action exerted upon the hypothalamus, pituitary, and the ovary are recommended using both animal and human models.

Disclosure

The author reports no conflicts of interest in this work.

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