Journal of Food Science, Kyoto Women's University No. 80 : 26–30 (2026)

Original Paper

Relationship between menstrual cycle and glucose metabolism in healthy young Japanese women

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Abstract

Background: The menstrual cycle, which is regulated by estrogen and progesterone, may influence glucose metabolism. Previous findings have remained inconsistent, and few studies have focused on Japanese women.

Methods: We investigated seven healthy young Japanese women with regular menstrual cycles (25–38 d). Each participant underwent a 75-g oral glucose tolerance test (OGTT) during both the follicular and luteal phases as determined by self-reported cycles. Fasting and post-load glucose and insulin levels were measured at 0, 30, 60, and 120 min. Estrogen, progesterone and HbA1c levels were also measured. Glucose tolerance was classified according to the Japan Diabetes Society criteria, and indices of insulin resistance (HOMA-IR), β-cell function (HOMA-β), and the insulinogenic index were evaluated.

Results: Estrogen and progesterone levels were significantly higher during the luteal phase than those during the follicular phase. Thirty minutes after glucose loading, plasma glucose values were high during the luteal phase (P=0.02), whereas insulin showed a tendency towards increasing values at 30 and 120 min (P=0.06). Although no significant differences were found in fasting indices of HOMA-IR or HOMA-β, the insulinogenic index was significantly lower during the luteal phase (P=0.03) compared to that during follicular phase.

Conclusions: The luteal phase is associated with impaired postprandial glucose handling and reduced early insulin secretion. Therefore, menstrual cycle phase should be considered when evaluating glucose metabolism in young premenopausal Japanese women.

Key words: menstrual cycle, oral glucose tolerance test (OGTT), insulin, estrogen, progesterone

(Received 7 October 2025, Accepted 18 October 2025)

I. Introduction

The menstrual cycle is a physiological process that occurs in women of the reproductive age. This was defined as the interval from the first day of menstruation to the day preceding the onset of the next menstrual cycle. It is divided into three phases: follicular, luteal, and menstrual. These phases are regulated by estrogen and progesterone secretion from the ovaries. The follicular phase refers to the period from the end of menstruation to ovulation, and is characterized by the predominant activity of estrogen, a hormone associated with follicular development. The luteal phase refers to the period from ovulation to the onset of menstruation, during which progesterone, a luteal hormone, is predominant.

Estrogen and progesterone affect glucose metabolism[1–3]. Previous reports assessing glucose metabolism in healthy women and considering the menstrual cycle, have yielded inconsistent results. Some studies have demonstrated differences between the follicular and luteal phases, whereas others have reported no significant variance [4].

The purpose of the present study was to investigate changes in glucose metabolism associated with the menstrual cycle by conducting oral glucose tolerance tests (OGTTs) in healthy young Japanese women during the follicular and luteal phases and to analyze variations in blood glucose and insulin levels.

II. Subjects and Methods

This study was conducted between the fiscal years 2022 and 2023. The participants were young healthy women from a university in Kyoto. Volunteers were recruited, and seven participants with self-reported regular menstrual cycles confirmed by basal body temperature measurements or a history of at least three consecutive cycles (25–38 d) were included in this analysis.

Follicular and luteal phases were estimated based on the

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self-reported last menstrual period and cycle length. Approximately at the middle of each phase, fasting blood samples were collected to measure estrogen (estradiol), progesterone, plasma glucose, and insulin levels in a 75-g oral glucose tolerance test (OGTT).

After a 10-h overnight fasting, blood samples were drawn to measure estrogen, progesterone, plasma glucose, insulin, and HbA1c levels. Subsequently, the participants ingested 75 g of glucose solution (TRELAN-G Oral Solution; A Y Pharmaceutical Co., Ltd.), and blood samples were collected at 30, 60, and 120 min to measure plasma glucose and insulin levels.

Glucose tolerance was classified according to the Japan Diabetes Society criteria[5]. Participants with a fasting plasma glucose (FPG) level of <110 mg/dL and a 120-min glucose level of <140 mg/dL were considered to have normal glucose tolerance. Those with FPG ≥126 mg/dL and/or 120-min glucose ≥200 mg/dL were classified as having diabetes, and all others were categorized as borderline.

To assess insulin resistance and β-cell function, three indices were calculated. Insulin resistance was estimated using the homeostatic model assessment for insulin resistance (HOMA-IR), defined as fasting insulin (μU/mL) multiplied by fasting plasma glucose (mg/dL) divided by 405. β-cell function was assessed using the homeostatic model assessment for β-cell function (HOMA-β), defined as fasting insulin (μU/mL) multiplied by 20 and divided by fasting plasma glucose (mg/dL) minus 63. Early phase insulin secretion was evaluated using the insulinogenic index, which is defined as the change in insulin concentration from 0 to 30 min divided by the change in glucose concentration during the same interval.

To further assess body composition and energy intake, height and weight were measured, and a brief self-administered diet history questionnaire (BDHQ) was completed on the day of the OGTT.

Normality of distribution was examined using the Shapiro–Wilk test. Normally distributed data are expressed as mean ± standard deviation, whereas the non-normally distributed data are expressed as medians (interquartile ranges). Paired comparisons were performed using Wilcoxon signed-rank tests. Statistical analyses were performed using SPSS version 28.0 (IBM, Armonk, NY, USA). A p-value <0.05 was considered statistically significant, and p <0.1 indicated a statistical trend.

The tests preceded by oral and written explanations and written informed consent was obtained from all participants. This study was approved by the Kyoto Women's University Clinical Research Ethics Committee (Approval No. 2021-40) and was conducted in accordance with principles of the Declaration of Helsinki.

III. Results

The participant characteristics are shown in Table 1. The median age was 22.0 years, and the menstrual cycle length was 29 ± 3 days. No significant differences were observed between the follicular and luteal phases in terms of body weight, BMI, fasting glucose, fasting insulin, or HbA1c. Estrogen and progesterone levels were significantly higher during the luteal phase than those during the follicular phase. Energy intake did not differ considerably between the phases.

In the 75-g OGTT results, six participants were classified as belonging to the normal and one to the borderline types during both phases. Figure 1 shows changes in plasma glucose levels during the OGTT. At 30 min post-load, the plasma glucose levels were significantly higher during the luteal phase than during the follicular phase (P=0.02). Figure 2 shows the changes in insulin levels during the OGTT. Insulin levels tended to be higher at 30 (P=0.06) and 120 min (P=0.06) during the luteal phase than those in the follicular phase. Figure 3 shows HOMA-IR, HOMA-β, and insulinogenic indices by each phase of menstrual cycle. HOMA-IR and HOMA-β showed no significant differences between phases, but the insulinogenic index was significantly lower during the luteal phase than that during the follicular phase (P=0.03).

Table 1. Characteristics of the subjects

N=7

	Follicular phase	Luteal phase	P value
Age (yrs)	22.0 (21.0, 24.0)		
Menstrual cycle (day)	29 ± 3		
Height (cm)	155.6 ± 4.5		
Body weight (kg)	49.7 ± 6.2	49.7 ± 6.2	0.85
Body mass index (BMI) (kg/m^2)	21.5 (18.7, 21.7)	21.7 (18.7, 21.7)	1.00
Fasting glucose levels (mg/dl)	98.9 ± 13.6	99.4 ± 8.8	0.61
Fasting insulin levels (μIU/mL)	6.6 ± 3.4	7.1 ± 3.1	0.87
HbA1c (%)	5.4 ± 0.3	5.5 ± 0.2	0.16
Estrogen (Estradiol) (pg/mL)	57.4 ± 26.3	181.9 ± 73.8	0.03*
Progesterone (ng/mL)	0.2 ± 0.1	11.5 ± 11.2	0.03*
Energy intake (kcal/day)	1568 ± 375	1471 ± 224	0.47

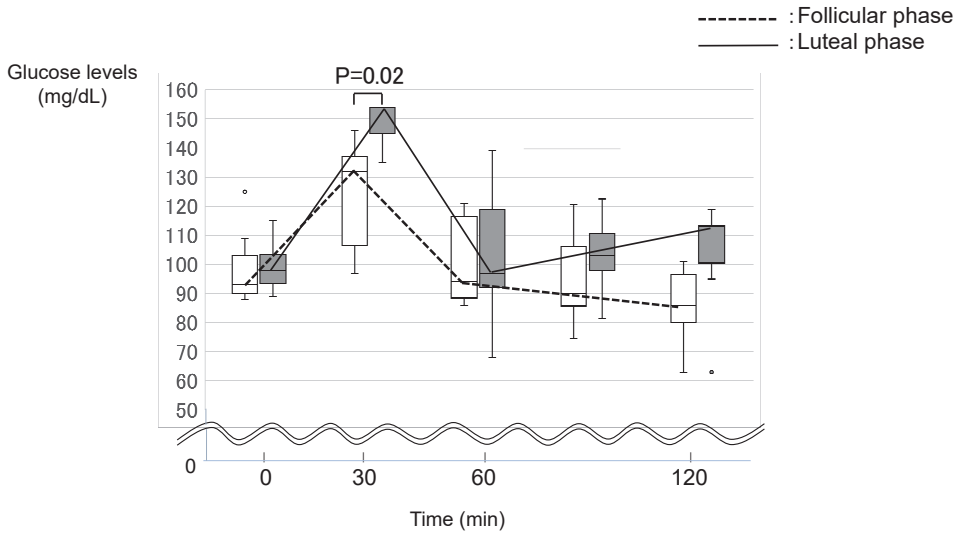

Figure 1. Changes in glucose levels in 75-g oral glucose tolerance test

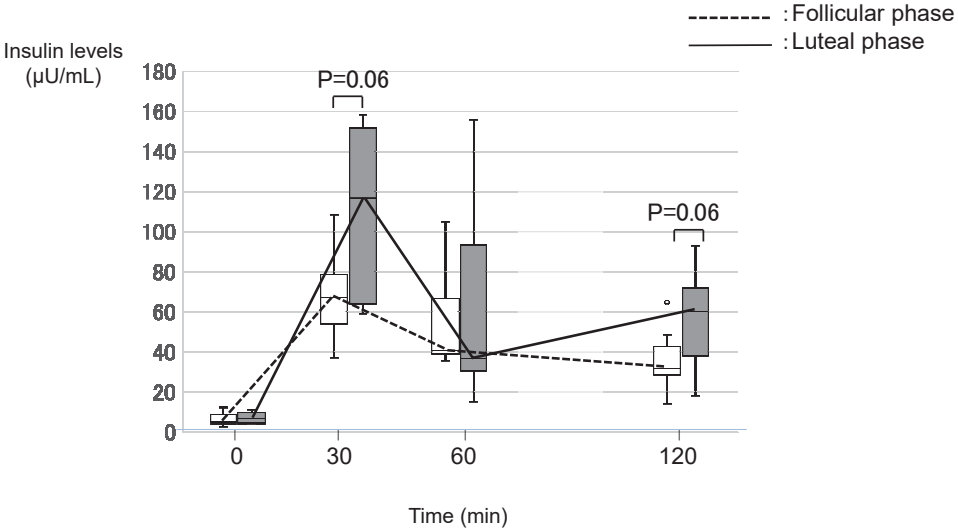

Figure 2. Changes in insulin levels in 75-g oral glucose tolerance test

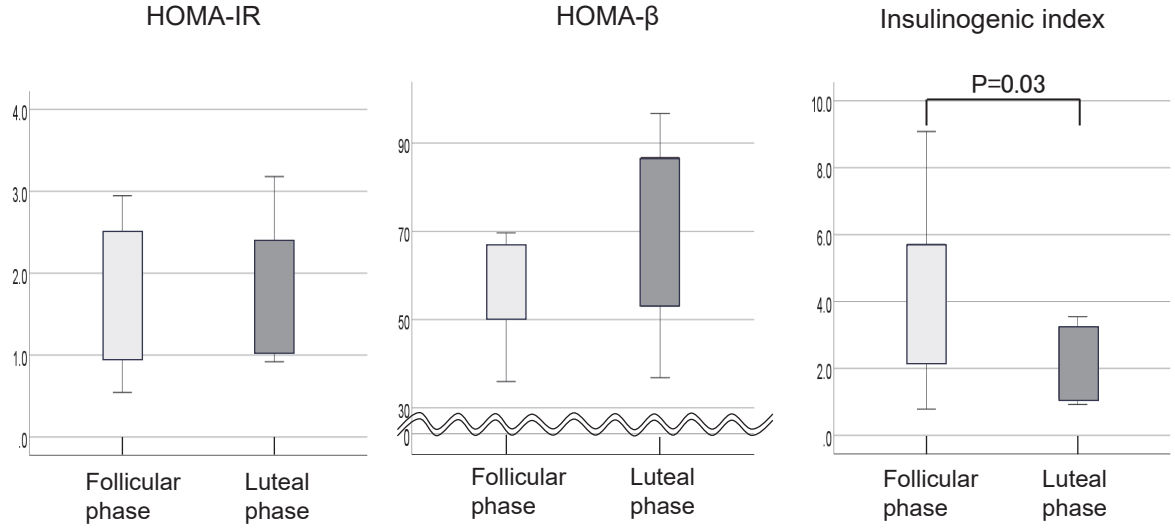

Figure 3. Insulin dynamics by each phase of menstrual cycle
HOMA-IR: homeostatic model assessment for insulin resistance
HOMA-β: homeostatic model assessment for β-cell function

IV. Discussion

In this study, healthy young Japanese women exhibited higher 30-min post-load glucose levels during the luteal phase than those during follicular phase, with insulin levels showing an upward trend at both 30 and 120 min. Although fasting indices of insulin resistance (HOMA-IR) and β-cell function (HOMA-β) showed no significant differences, the insulinogenic index was significantly reduced during the luteal phase. These findings suggest that relative post-load insulin resistance and reduced additional insulin secretion contribute to elevated postprandial glucose levels during the luteal phase.

The effects of female hormones on insulin secretion are mediated by diverse metabolic, genomic, endocrine, and immunological pathways, and remain poorly understood[4]. Possible mechanisms include the direct action of estrogen and progesterone on pancreatic receptors[6] and modulation of glucose uptake via glucose transporters[7]. Estrogen (estradiol) enhances insulin sensitivity in the skeletal muscle, liver, and adipose tissue, while regulating inflammation and lipid metabolism. In contrast, progesterone impairs insulin signaling and inhibits GLUT4 translocation[3]. Experimental studies in female rats have shown that estrogen enhances insulin sensitivity, whereas progesterone contributes to its reduction[8]. Progesterone has been reported to induce insulin resistance by impairing insulin signaling in 3T3-L1 adipocytes[9] and inhibiting glucose uptake in the skeletal muscle and adipose tissue in rats[10, 11]. Collectively, these studies indicated that estrogen improves glucose metabolism, whereas progesterone impairs it.

However, studies in humans that have considered menstrual cycles have yielded inconsistent results. Walsh et al.[12] reported that in 33 women (mean age 23 years), glucose and insulin levels peaked at menstruation and were significantly higher at 0 and 30 min in weekly 50-g OGTTs across four weeks. In contrast, Cudworth et al.[13] tested 20 women (mean age 19 years) with 100-g OGTTs during the follicular, luteal, and premenstrual phases and found no differences in glucose or insulin levels. Bennal et al.[14] examined 50 young normal-weight women and found significantly higher 2-h glucose levels during the luteal phase than those during the follicular phase. Williams et al.[15] performed two 75-g OGTTs in 17 women with regular cycles timed using ovulation kits and found no significant differences in glucose or insulin levels. A Japanese study on 21 young women who underwent a 75-g OGTT on days 8–10 (follicular phase) and 19–23 (luteal phase) found no significant differences[16]. Bonora[17] and Busby[18] divided women into separate groups according to the cycle phase and reported no glucose differences; however, these two studies were not within-subject comparisons.

Brennan et al.[19] found no fasting differences in glucose or insulin between menstrual cycle phases in nine women (mean age 31 years) but found significantly higher glucose and insulin levels during the luteal phase at 30 min after 50-g OGTT. Intravenous glucose tolerance test (IVGTT) evaluations have reported lower insulin sensitivity during the luteal phase than that during the follicular phase[20, 21], whereas clamp studies have not found any phase differences[22]. In our research, luteal-phase post-load glucose and insulin levels increased, and the insulinogenic index decreased, suggesting post-load insulin resistance.

Notably, our results showed higher estrogen levels during the luteal phase. Jensen et al.[23] reported that estrogen levels peaked before ovulation and slightly increased during the early to mid-luteal phases, whereas progesterone levels rose near ovulation, peaked during the mid-luteal phase, and then declined. Thus, differences in sampling timing may explain the inconsistencies across studies. Future research should employ basal body temperature, ovulation kits, or luteinizing hormone (LH) surge detection combined with estrogen and progesterone measurements to accurately define the cycle phases.

Trout et al.[24] reported that insulin sensitivity decreases with worsening premenstrual symptoms. Women with premenstrual syndrome (PMS) often exhibit elevated high-sensitivity C-reactive protein (CRP) and inflammatory cytokine levels during the luteal phase[25]. Therefore, future studies on menstrual cycle-related glucose metabolism should consider other metabolic dynamics.

This study has some limitations. First, although all participants had regular cycles, the follicular and luteal phases were determined by self-reporting, which may not have ensured a precise classification. Second, the sample size was small and limited to young women, which restricts the generalizability of the results. Third, background factors other than BMI and diet were not considered.

Despite these limitations, our findings suggest that post-load glucose levels increase during a luteal phase without changes in fasting glucose levels. Therefore, menstrual cycle phase should be considered when evaluating glucose metabolism in premenopausal women. Further detailed studies including different age groups and mechanistic analyses are warranted.

Acknowledgments

We sincerely thank the students of the Department of Food and Nutrition, Kyoto Women's University, for their cooperation in this study.

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