Glucose kinetics and exercise performance during phases of the menstrual cycle: effect of glucose ingestion

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Campbell, S. E., D. J. Angus, and M. A. Febbraio. Glucose kinetics and exercise performance during phases of the menstrual cycle: effect of glucose ingestion. Am J Physiol Endocrinol Metab 281: E817–E825, 2001.—To study the effect of menstrual cycle phase and carbohydrate ingestion on glucose kinetics and exercise performance, eight healthy, moderately trained, eumenorrheic women cycled at 70% of peak O₂ consumption for 2 h and then performed a 4 kJ/kg body wt time trial. A control (C) and a glucose ingestion (G) trial were completed during the follicular (F) and luteal (L) phases of the menstrual cycle. Plasma substrate concentrations were similar before the commencement of exercise. Glucose rates of appearance and disappearance were higher (P < 0.05) during the 2nd h of exercise in FC than in LC. The percent contribution of carbohydrate to total energy expenditure was greater in FC than in LC, and subjects performed better (13%, P < 0.05) in FC. Performance improved (19% and 26% in FG and LG compared with FC and LC, respectively, P < 0.05) with the ingestion of glucose throughout exercise. These data demonstrate that substrate metabolism and exercise performance are influenced by the menstrual cycle phase, but ingestion of glucose minimizes these effects. 

Although traditionally known for their role in reproduction, the ovarian hormones are also thought to exert significant metabolic effects. Studies in animals have consistently demonstrated that 17β-estradiol (E₂) is a potent promoter of increased lipid oxidation during endurance exercise (18, 22), resulting in a sparing of muscle glycogen (22). This effect has also been seen in humans (16, 35), although not consistently (15). In contrast, progesterone is known to reverse many “estrogenic” effects, including increased fat oxidation (18). Levels of progesterone are 12–20 times greater during the luteal phase than during the follicular phase, whereas estrogen is only ~3 times greater (24). Hence, varying levels of these hormones throughout the menstrual cycle could alter skeletal muscle metabolism during exercise.

Previous studies investigating exercise metabolism in different phases of the menstrual cycle have produced equivocal results. Several studies investigating short- 

term or intermittent exercise have found no differences between the follicular and the luteal phase (11, 27). Additionally, two studies have found no phase effect on metabolism during prolonged exercise of ≥90 min (3, 21). Conversely, a number of studies have found that menstrual cycle phase does indeed affect hormonal and metabolic response to exercise (16, 19, 26, 29), particularly in a carbohydrate (CHO)-depleted nutritional state (4, 25).

This study investigated the metabolic requirements and glucose kinetics during prolonged exercise in women in the presence and absence of glucose ingestion. Additionally, we sought to determine whether glucose ingestion increases exercise performance in a race-type (time trial) setting and whether metabolism and exercise performance, with and without glucose supplementation, are influenced by the phase of the menstrual cycle. We hypothesized that menstrual cycle phase would affect exercise metabolism, with elevated levels of the ovarian hormones in the luteal phase decreasing CHO oxidation during exercise. Furthermore, we hypothesized that because women use more fat and less CHO than their male counterparts (15, 36), the benefits of glucose supplementation would not be as marked as previously demonstrated in men (2, 9). Recently, Bailey et al. (3) demonstrated that, compared with a placebo, ingestion of CHO increased time to fatigue in the follicular and luteal phases, indicating that it is beneficial in some parameters of exercise. However, the reasons for the onset of fatigue remain elusive and are likely to include factors other than metabolism, such as neurological responses to exercise (10). Consequently, fatigue is perhaps not the best parameter to use when determining the metabolic effects of the ovarian hormones. Evaluation of the effect of CHO ingestion on glucose kinetics and exercise performance using a time trial model will provide new information on glucose metabolism during prolonged exercise in women.

METHODS

Subjects. Eight healthy, nonsmoking, endurance-trained women with a peak O₂ consumption (VO₂ peak) of ≥50 ml·kg⁻¹·min⁻¹ volunteered as subjects for the study. Subjects were eumenorrheic and were not taking any oral con-
tracers for ≥6 mo before testing. Each subject was made fully aware of the procedures and risks associated with the study, both verbally and in writing. All subjects completed a medical and a menstrual questionnaire and provided written informed consent. This experiment was approved by The University of Melbourne Human Research Ethics Committee.

Preexperimental protocol. To analyze the menstrual cycle before the commencement of trials, subjects collected daily urine samples for determination of estrone glucuronide and pregnanediol glucuronide concentrations, urinary metabolites of estrogen and progesterone (6). This ensured appropriate changes in hormone levels between the follicular and luteal phases of their menstrual cycle and allowed for accurate determination of each subject’s menstrual cycle duration. Additionally, blood samples taken before the commencement of exercise were analyzed for E2 and progesterone to further check menstrual phase and status.

During the follicular phase before the first exercise trial, a V˙O2peak test was performed on an electromagnetically braked cycle ergometer (LODE Instrument, Groningen, The Netherlands). A familiarization trial was also completed during the menstrual cycle preceding experimental trials to allow subjects to become comfortable with the laboratory setting and the experimental protocol. In the 24 h before the V˙O2peak test, the familiarization trial, and all experimental trials, subjects were instructed to refrain from strenuous exercise, alcohol, tobacco, and caffeine. Before the four experimental trials, subjects were provided with food parcels (12.6 MJ; 71% CHO, 15% protein, and 14% fat) to be consumed on the day preceding each trial. No food was permitted on waking on the morning of an experimental trial. Subjects were instructed to strictly adhere to the diet and were permitted to consume only water ad libitum. These pretrial exercise and lifestyle controls helped ensure that hormonal and metabolite values were stable and similar for each subject before each experimental trial.

Experimental trials. Four experiments were conducted over the course of at least two menstrual cycles, with each test occurring at a specific time during the menstrual cycle, previously determined for each subject by urinalysis. The menstrual phases were confirmed by urinalysis on the morning of each experimental trial. To avoid confounding phase effect with test order, subjects were randomly allocated to different test orders, with four subjects commencing in the follicular phases, with a 2.5-fold increase in E2 (P < 0.01) and a 18-fold increase in progesterone (P < 0.01) in the luteal phase compared with the follicular phase. As expected, no

Table 1. Subject characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
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<tbody>
<tr>
<td>Age, yr</td>
<td>24 ± 2</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>61.0 ± 2.2</td>
</tr>
<tr>
<td>Height, cm</td>
<td>169.1 ± 2.8</td>
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<tr>
<td>V˙O2peak, l/min</td>
<td>3.3 ± 0.2</td>
</tr>
<tr>
<td>ml·kg·1·1·1</td>
<td>53.5 ± 0.9</td>
</tr>
</tbody>
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Values are means ± SE; n = 8. V˙O2peak, peak O2 consumption.
differences were found in hormone levels between control and glucose trials conducted in the same phase of the menstrual cycle. Heart rate was not different at any point between trials (data not shown). Characteristics for each of the four experimental trials are presented in Table 2. Because we assume that glucose rate of disappearance (Rd) during exercise was approximately equal to the amount of glucose oxidized, we were able to obtain an indirect measure of glucose oxidation and CHO oxidation derived from other sources (i.e., glycogen) (20). There were no differences in the average percent $V_{\text{o2peak}}$ or total energy expenditure in any of the trials. The total percent contribution of CHO was higher in FC than in LC ($P < 0.05$) and was even greater in the glucose trials ($P < 0.05$). Additionally, the ingestion of glucose throughout exercise increased the percent contribution of plasma glucose vs. other CHO compared with both control trials ($P < 0.05$). There was also a trend for increased contribution of plasma glucose in FC compared with LC; however, this did not reach statistical significance ($P = 0.058$).

**Plasma hormones and metabolites.** There were no differences in plasma glucose or lactate concentrations before the commencement of exercise in any of the experimental trials (Fig. 2). Glucose ingestion increased plasma glucose levels to above resting values ($P < 0.05$) at all time points during exercise in the follicular and luteal phases. During both control trials (FC and LC) there was a gradual decline in plasma glucose levels that became significantly different from rest at 120 min of exercise. Menstrual cycle phase had no effect on plasma glucose concentrations during exercise in the placebo trials; however, in the glucose trials, plasma glucose was higher at 30 and 60 min in FG than in LG. Plasma lactate concentrations were elevated above resting values throughout exercise ($P < 0.05$), but neither glucose ingestion nor menstrual cycle phase had any effect.

Plasma FFA and glycerol levels were also similar before the commencement of exercise in all trials (Fig. 3). Plasma FFA concentrations were increased compared with resting values ($P < 0.05$) at 60 and 90 min of exercise in the FC and LC trials, respectively, to the end of steady-state exercise (120 min). Exercise also increased plasma glycerol levels ($P < 0.05$) to above resting values at 30 min (FC), 60 min (FG and LC), and 90 min (LG). Plasma FFA and glycerol concentrations were elevated ($P < 0.05$) in FC compared with LC at all time points during exercise. Ingestion of glucose during exercise suppressed plasma FFA and glycerol levels in the 2nd h of exercise ($P < 0.05$) compared with the control trial in both phases of the menstrual cycle.

Although plasma insulin values were not significantly different before exercise, there was a tendency ($P = 0.07$) for higher basal plasma insulin in the luteal phase (Fig. 4). There was a phase effect at 30 min of exercise in the glucose trials, with insulin being ele-
A

FG and LG

Fig. 2. Plasma glucose (A) and lactate (B) concentrations at rest and during 2 h of cycling exercise in different phases of the menstrual cycle with or without a CHO beverage. F, follicular phase; L, luteal phase; C, control; G, glucose ingestion. *Different (P < 0.05) from resting values from that point onward. †Difference (P < 0.05) between FC and LC at the same time point. ‡Difference (P < 0.05) between FG and LG at the same time point. §Difference (P < 0.05) between FC and FG at the same time point. ¶Differences (P < 0.05) between LC and LG at the same time point.

B

All groups

Fig. 3. Plasma free fatty acid (FFA, A) and glycerol (B) concentrations at rest and during 2 h of cycling exercise in different phases of the menstrual cycle with or without a CHO beverage. See Fig. 2 legend for explanation of symbols.

was a result of increased HGP in the control trials (FC and LC); however, in the glucose trials (FG and LG), HGP was suppressed (P < 0.05) compared with control trials and resting values, and the $R_a$ was maintained primarily by absorption of glucose by the gut. As expected, despite the suppressed HGP, total glucose $R_a$ was higher in the glucose trials (P < 0.05) than in the control trials regardless of menstrual cycle phase. Interestingly, HGP and glucose $R_a$ were elevated (P < 0.05) beginning at 30 and 75 min, respectively, in FC compared with LC. Although HGP was higher and gut $R_a$ was lower in LG than in FG at 15 min of exercise (P < 0.05), there were no other phase effects on total $R_a$, gut $R_a$, or HGP with the ingestion of glucose during exercise.

Glucose $R_d$ and the metabolic clearance rate (MCR) were increased during exercise in all trials (Fig. 6). Glucose $R_d$ was increased during the glucose trials compared with the control trials (P < 0.05) starting at 30 and 60 min in the follicular and luteal phases, respectively. During the control trials, $R_d$ was significantly higher (P < 0.05) in FC than in LC during the 2nd h of exercise. These phase effects were not seen in glucose trials (FG and LG). Although there were no specific differences in MCR, there was a phase × drink...
interaction, with glucose ingestion increasing MCR and higher MCR in FC than in LC ($P < 0.05$).

**Performance.** Figure 7 illustrates the performance times for the four trials, demonstrating that glucose ingestion decreased ($P < 0.05$) the time taken to complete the set amount of work, regardless of menstrual cycle phase (19 and 26% improvement in FG and LG compared with FC and LC, respectively, $P < 0.05$). Additionally, subjects completed the work faster in FC than in LC (13% improvement, $P < 0.05$). Interestingly, this menstrual phase performance difference was abolished by the ingestion of glucose during exercise.

**DISCUSSION**

The results of the study demonstrate that variations in the ovarian hormone levels throughout the menstrual cycle do alter exercise metabolism, but only in the absence of glucose ingestion. Indeed, as the control trials progressed, differences became more pronounced, indicating that as CHO sources became more depleted, the influence of the sex steroids on exercise metabolism became more evident. This was further exemplified by the lack of differences between FG and LG trials. When CHO was adequately supplied throughout exercise, the cycling levels of E$_2$ and progesterone had only a minimal effect.

Glucose kinetic data revealed that, during control trials, $R_a$, HGP, and $R_d$ were lower in LC, particularly during the 2nd h of exercise. These findings were similar to another recent study (39), despite differences in the exercise protocol. Subjects in the previous study (39) exercised at much lower intensities, when larger differences in substrate oxidation might be expected. Recently, two other studies have investigated the effect of E$_2$ on glucose kinetics: one examined treatment of amenorrheic women with transdermal E$_2$ patches (33), and the other gave short-term oral E$_2$ treatments to men (8). In both studies, E$_2$ reduced $R_a$ and $R_d$; however, results from these studies must be carefully interpreted. Amenorrhea itself brings about metabolic changes, which may alter responses to exercise (23) and could additionally change the response to artificially increased levels of E$_2$. Furthermore, the treatment of amenorrhea with E$_2$ resulted in plasma E$_2$ levels that were still $>10$-fold less than those seen in

![](image1)

**Fig. 4.** Plasma insulin (A) and glucagon (B) concentrations at rest and during 2 h of cycling exercise in different phases of the menstrual cycle with or without a CHO beverage. See Fig. 2 legend for explanation of symbols.

![](image2)

**Fig. 5.** Total rate of glucose appearance ($R_a$, A) and hepatic glucose production (HGP, B) at rest and during 2 h of cycling exercise in different phases of the menstrual cycle with or without a CHO beverage. See Fig. 2 legend for explanation of symbols.
normally menstruating women and, therefore, may not be relevant to eumenorrheic athletes. Correspondingly, although treating men with E2 can provide interesting results because of differences in receptor populations and a number of other physiological variables, men and women often respond differently to changes in the sex steroids (17). Thus, despite the temptation to relate the decreased Ra and Rd during the luteal phase in this study to elevated E2 levels, this has not been experimentally confirmed.

The percent contribution of CHO and fat to total substrate oxidation was significantly different between the control trials. During FC, the percent contribution from CHO was greater and that from fat was less than during LC. Additionally, glucose Ra was greater throughout exercise in FC than in LC, and this corresponded with a strong tendency (P = 0.058) for greater glucose oxidation. This small increase in Rd resulted in a decrease in fat oxidation rather than an attenuated use of other CHO (i.e., glycogen). However, glycogen was not directly measured. In a recent study that did measure muscle glycogen use, Hackney (16) demonstrated that glycogen use is decreased in the luteal phase compared with the follicular phase during 60 min of cycling exercise. Discrepancies in these results are probably due to the sensitivity of whole body pulmonary and tracer-determined measures to derive glycogen oxidation, which is a limitation in this study. However, differences could also be due to the duration of exercise; in this study, differences in Rd were found after 60 min of exercise. This could indicate that, during FC, as muscle glycogen stores become depleted, glucose uptake is increased, allowing for sparing of glycogen during the later stages of exercise. Interestingly, in this study, differences in substrate oxidation between the two phases lie primarily in glucose uptake and utilization and lipid oxidation. This could result from preferential oxidation of one substrate over the other or from preferential uptake of glucose or FFA from circulation. From these results, it is impossible to determine whether the source of fat for oxidation was intramuscular triglycerides or uptake of plasma FFA. Given the recent findings of plasma membrane and cytosolic fatty acid transport proteins (5), it would be interesting to further investigate menstrual phase effects on lipid kinetics during exercise.

The metabolic effects of E2 have been a subject of great interest, particularly in lipid synthesis and oxidation. Accordingly, the increased reliance on fat oxidation observed during the luteal phase has been readily attributed to the concurrent elevation in E2. However, during the luteal phase, there is a proportionately much greater increase in progesterone concentrations, which itself could have metabolic effects. Progesterone has often been reported to have an “antiestrogenic” effect, which has been observed in CHO and lipid metabolism (18, 34). Animal studies have demonstrated that E2 spares glycogen during prolonged exercise, likely due to increased lipid availability and oxidation (22). Unfortunately, these studies did...
not investigate the effect of progesterone alone or in combination with E2. Interestingly, E2 has also been demonstrated to have beneficial effects in CHO metabolism, increasing glucose uptake stimulated by insulin (31) and exercise (7). Although progesterone alone has often been reported as having no distinct effects on lipid or CHO metabolism in ovariectomized animals (31), when progesterone and E2 have been administered in combination, progesterone has inhibited the beneficial effect of E2 on lipid availability and oxidation (18) and CHO metabolism (31). These combined findings suggest that the menstrual phase effects on exercise metabolism in the placebo trials could result from elevated progesterone levels in LC inhibiting the beneficial effects of E2 on glucose uptake, thereby forcing the contracting muscles to increase fat oxidation. CHO oxidation requires less O2 per joule than fat and is the substrate of choice during exercise of moderate to high intensity (32). Because the exercise intensity used in this investigation (~70% \( \dot{V}O_2 \) peak) was at a level at which CHO metabolism may become exponentially more important to energy production, it is likely that glucose uptake would play a greater role in this protocol. Furthermore, increased glucose uptake could be responsible for the increase in performance during the FC trials. The time trial protocol allowed athletes to determine their own pace during the completion of the set amount of work (simulating a race situation). Every subject performed faster in FC than in LC, indicating that they were able to maintain a higher intensity of exercise throughout the time trial. As reliance on CHO increases with exercise intensity (32), it seems logical that an increased ability for glucose uptake during FC would benefit performance. Interestingly, we recently demonstrated that progesterone decreases total GLUT-4 content in the red vastus of rats (unpublished data), which would restrict glucose uptake during the luteal phase, particularly during increased metabolic stress. Although greater time to exhaustion has been previously observed in the luteal than in the follicular phase (29), inasmuch as subjects must ride at a previously determined workload, an increased ability for glucose uptake may not be as advantageous. However, even this phase effect seems to also be contingent on nutritional status, inasmuch as time to fatigue was similar with glucose ingestion (3).

Further evidence to suggest the preferential oxidation of CHO at the exercise intensity used in this study is the reduction in fat oxidation with glucose ingestion. This could be due to elevated insulin levels suppressing lipolysis (38), thereby decreasing lipid availability; however, it could also be the result of increased CHO availability. When plasma glucose levels are elevated, there is a larger concentration gradient for glucose to move into the cell, perhaps limiting the effect of the ovarian hormones on glucose transport. Although plasma glucose levels were similar between FC and LC, they were significantly lower than during the glucose trials, perhaps increasing the importance of glucose transport capacity. Notably, the difference in glucose \( R_d \) between FC and LC persisted throughout the 2nd h of exercise, even in the presence of similar plasma glucose concentration. This resulted in a lower MCR in LC (\( P < 0.05 \)), suggesting that the reduced glucose disposal was due to a decrease in glucose transport per se and not to relative hypoglycemia. Although glucose \( R_a \) and \( R_d \) were statistically different in FC and LC only during the 2nd h of exercise, HGP was higher in FC than in LC beginning at 30 min. This is perhaps indicative of subtle differences in glucose \( R_a \) and \( R_d \) before 60 min of exercise. Finally, elevation of glucose \( R_d \) during the 2nd h of exercise in FC compared with LC supports the hypothesis that the metabolic changes resulting from variations in the ovarian hormones were caused by progesterone inhibiting the effect of E2 on glucose uptake.

Ingestion of glucose obliterated most of the metabolic differences between follicular and luteal phase trials; however, it produced some interesting effects on glucose kinetics. This is the first study to investigate glucose kinetics during CHO ingestion in women, despite previously observed gender differences in CHO metabolism during exercise (35, 36). Ingestion of glucose during exercise resulted in an increase in glucose \( R_a \), but most interestingly, it also resulted in an increase in plasma glucose oxidation. The increase in the percent contribution to energy expenditure of plasma glucose resulted in a shift of substrate oxidation from fat to CHO in FG and LG compared with control trials. Additionally, it resulted in a small, but significant, decrease in the oxidation of other CHO compared with control trials, possibly indicating a glycogen-sparing effect. These results differ from those previously seen in men (20, 28), where the contribution of plasma glucose to total CHO oxidation was not substantial. It is interesting to note that a similar exercise/CHO ingestion protocol on men conducted in our laboratory demonstrated that plasma glucose contributed only 8–11% to substrate oxidation during CHO ingestion (12). Conversely, in the present study, there was a 9–12% contribution during the control trials, and this increased to 19% in the glucose trials. Furthermore, despite glucose ingestion altering glucose kinetics in men, it has been demonstrated to have no effect on glycogen use during exercise (13, 20). Although this gender comparison is anecdotal, this is not the first study to observe a greater glucose flux in women than in men. Friedlander et al. (14) found that, after training, a higher percentage of total CHO oxidation was derived from plasma glucose in women and that this likely resulted in glycerogen sparing compared with their male counterparts. These findings suggest that trained women have a greater capacity to utilize plasma glucose during exercise and, therefore, may derive a greater benefit from CHO ingestion than that previously seen in men. Indeed, a previous study from our laboratory using a time trial protocol found that glucose ingestion resulted in a 7% increase in performance in men (2), whereas this study reports a 19–26% increase in performance, notwithstanding the differences in time trial protocols when these two studies are compared.
The effect of menstrual cycle phase on exercise performance is of particular importance to female athletes. This study has demonstrated that, in the fasted state, women perform better in the follicular than in the luteal phase of the menstrual cycle. However, the ingestion of glucose obliterated this phase difference, illustrating that, in the postprandial state, the metabolic stress of endurance exercise is not sufficient to elicit menstrual phase effects. This could possibly explain some of the discrepancy in the literature with regard to the effect of menstrual cycle phase on exercise performance. In a recent study reporting an absence of metabolic differences between the follicular and luteal phases during endurance exercise to fatigue, the trials were conducted in the postprandial state (3).

Additionally, although Kanaley et al. (21) also reported no effect of menstrual phase during 90 min of endurance exercise, they investigated only substrate utilization based on the nonprotein respiratory quotient and did not have a performance component. This result is similar to the results observed in this study up to 60 min; however, we found that glucose kinetics and substrate oxidation did indeed vary, particularly during the 2nd h of exercise. On the basis of the results from this study, female athletes preparing for races during the luteal phase of their menstrual cycle should ensure adequate CHO consumption during an endurance event. Finally, these results are also important for researchers investigating metabolic responses to exercise in women, inasmuch as they demonstrate that variations in exercise metabolism induced by the menstrual cycle can be minimized by ensuring an adequate CHO source throughout endurance exercise.

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REFERENCES