Alterations in Glucose Metabolism During Menstrual Cycle in Women With IDDM

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OBJECTIVE— To examine the hormonal mechanisms underlying the variability in glycemic control during the different phases of the menstrual cycle in women with insulin-dependent diabetes mellitus (IDDM).

RESEARCH DESIGN AND METHODS— Hyperglycemic (11.7 ± 0.1 mM), hyperinsulinemic (24 ± 3 mU/L) clamp studies were performed in 16 women with IDDM during the follicular (day 8 ± 1) and luteal (day 23 ± 1) phases of the menstrual cycle. Seven of the patients (group 1) experienced worsening glucose control during the luteal phase, whereas nine patients (group 2) did not.

RESULTS— In group 1, glucose metabolism fell from 30.2 ± 3.8 $\mu mol \cdot kg^{-1} \cdot min^{-1}$ during the follicular phase to 24.5 ± 2.0 $\mu mol \cdot kg^{-1} \cdot min^{-1}$ during the luteal phase ($P = 0.09$), whereas in group 2 it increased from 18.5 ± 1.2 to 23.2 ± 2.3 $\mu mol \cdot kg^{-1} \cdot min^{-1}$ ($P = 0.03$). The decrease in glucose metabolism during the luteal phase in patients in group 1 was associated with a significant rise in the serum estradiol levels from the follicular to luteal phase (164 ± 39 vs. 352 ± 59 pM, $P = 0.006$), whereas this rise was not observed in group 2 (334 ± 156 vs. 423 ± 74 pM, NS). Changes in other reproductive hormones (progesterone, testosterone, dihydrotestosterone, androstenedione, luteinizing hormone, follicular-stimulating hormone, or prolactin) were not related to the differences in glucose uptake in the two groups.

CONCLUSIONS— *1*) Marked heterogeneity in glucose metabolism is seen throughout the menstrual cycle in women with IDDM, 2) a subgroup of patients exhibits worsening premenstrual hyperglycemia and a decline in insulin sensitivity during the luteal phase, and 3) the deterioration in glucose uptake in this subgroup was associated with a greater increment in estradiol levels from the follicular to the luteal phase.

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Several reports have demonstrated a worsening of glycemic control during the luteal phase of the menstrual cycle in women with insulin-dependent diabetes mellitus (IDDM) (1–3). Studies examining this phenomenon, however, have yielded conflicting results. In healthy nondiabetic women, some investigators have reported a worsening in glucose tolerance, as assessed by the oral glucose tolerance test (OGTT), during the luteal phase (4,5). However, other studies that used the OGTT (6,7) or the intravenous glucose tolerance test (8) did not find significant changes in glucose tolerance or insulin concentration as a function of the menstrual cycle phase. Evaluation of insulin sensitivity by means of the euglycemic-hyperinsulinemic clamp technique has also failed to detect alterations during the luteal phase in nondiabetic women (9,10).

We recently examined glucose homeostasis in healthy women during the follicular and luteal phases of the menstrual cycle with the hyperglycemic clamp technique (11). This method permits quantitation of tissue glucose uptake in response to a hyperglycemic hyperinsulinemic stimulus. We found that basal and glucose-stimulated insulin responses were similar in the follicular and luteal studies. However, glucose uptake and the ratio of glucose uptake to insulin concentration were both significantly lower during the luteal phase. These data suggest that the observed defects in glucose utilization may reflect an impairment in the ability of hyperglycemia per se to enhance glucose disposal during the luteal phase. Therefore, this study was undertaken to determine whether women with IDDM who experience a deterioration in glycemic control during the luteal phase also exhibit a reduction in glucose uptake when measured under similar hyperglycemic conditions.

RESEARCH DESIGN AND METHODS

METHODS— Sixteen women with IDDM and regular menstrual cycles

were studied. The subjects were between the ages of 18 and 38 yr (mean ± SD 29 ± 5 yr) with a diabetes duration of 2–30 yr (mean ± SD 18 ± 8 yr) and body mass index of 20–33 kg/m^2 (mean ± SD 24 ± 3 kg/m^2). The total daily insulin dose was 26–60 U/day with a mean of 40 ± 9 U/day. Total glycosylated hemoglobin in the subjects ranged from 7.5–15.4% (mean ± SD 10.3 ± 2.4%, nondiabetic normal range 5.4–7.4%). The mean length of the menstrual cycle was 29 ± 3 days (range 24–38 days). No subject was receiving oral contraceptive pills or any medication (other than insulin) known to influence glucose metabolism.

Seven of the subjects (group 1) exhibited premenstrual hyperglycemia as evidenced by a consistent increase in self-monitored blood glucose results during the week before menses. In addition, three of the seven patients increased their insulin dose (mean increment 3 ± 1 U/day) during the late luteal phase. In the other nine subjects (group 2), premenstrual hyperglycemia was absent. Eight of these patients reported no change in glucose control before menses, whereas one noted an increased frequency of hypoglycemia. The mean menstrual cycle length did not differ in group 1 (29 ± 3 days) versus group 2 (29 ± 4 days).

Subjects were studied during the midfollicular and midluteal phases of the menstrual cycle. The follicular phase studies were performed on cycle days 5–11 (average day 8 ± 1 or 22 ± 3 days preceding the next menstrual period) and the luteal phase studies on days 20–29 (average day 23 ± 1 or 7 ± 1 days preceding the next menstrual period). Voluntary written informed consent was obtained from each subject, and the experimental protocol was approved by the Joslin Diabetes Center Committee on Human Studies.

Two hyperglycemic clamp studies were performed in each subject in random order—one during the follicular phase and one during the luteal phase of the menstrual cycle. Eight patients received the follicular phase study first, whereas eight received the luteal phase study first. Studies were conducted after a 10- to 12-h overnight fast. The subjects received their usual dose of subcutaneous insulin the day before the study, but omitted their insulin on the study mornings. The study was postponed to another day if hypoglycemia (symptomatic or measured glucose <3.3 mM) occurred during the preceding 24 h. On the morning of the study a catheter was inserted into an antecubital vein for the administration of insulin and glucose, and a second catheter was placed in retrograde manner into a vein on the dorsal portion of the hand or wrist for blood sampling. The hand was placed in a box heated to 70°C to ensure arterialization of venous blood (12).

The plasma glucose concentration was initially stabilized between 4.6 and 9.5 mM (mean 7.8 ± 0.3 mM) for 60 min with an insulin infusion of 0.24 ± 0.02 mU · kg^{-1} · min^{-1}. After the collection of baseline samples, a primed continuous infusion (0.5 mU/kg · min) of crystalline insulin (Lilly, Indianapolis, IN) was administered for 2 h. This insulin dose was selected as that which would yield plasma insulin levels in the same range observed in nondiabetic subjects undergoing a hyperglycemic clamp (11). The hyperglycemic glucose-clamp technique (13) was used to acutely raise the plasma glucose concentration to a target level of 11.7 mM and maintain it at this level for 2 h. A priming dose of a 20% glucose solution was administered over the first 15 min. Subsequently, the glucose infusion rate was adjusted to maintain the plasma glucose concentration at the target level based on arterialized plasma glucose measurements.

Plasma glucose was determined at 2-min intervals during the first 10 min of the hyperglycemic clamp and at 5-min intervals thereafter. Plasma for free insulin measurement was drawn in the basal state and at 20-min intervals during the clamp study. Three blood samples were drawn during the basal period during each study and the plasma pooled for determination of estradiol, progesterone, luteinizing hormone (LH), follicular-stimulating hormone (FSH), prolactin, testosterone, dihydrotestosterone, and androstenedione.

Under steady-state hyperglycemic conditions, as occurs during the final hour of the hyperglycemic clamp, hepatic glucose production is suppressed (14,15). Therefore, the glucose disposal rate (M) was measured as the glucose infused during the last 60 min of the insulin clamp corrected for urinary glucose losses. Luteal phase studies were included in the analysis only if ovulation was subsequently confirmed by a rise in serum progesterone level.

Analytical procedures

Plasma glucose was measured at the bedside by the glucose oxidase method with a YSI glucose analyzer (Yellow Springs, OH). Free insulin was measured by treating the plasma samples initially with polyethylene glycol to precipitate antibody-bound insulin and then performing a double-antibody radioimmunoassay (16). Total glycosylated hemoglobin was measured by agar gel electrophoresis with removal of the labile component with the GLYTRAC glycosylated hemoglobin kit (Corning, Palo Alto, CA) (17). LH, FSH, estradiol, progesterone, and prolactin levels were determined by radioimmunoassay (18–20). Serum testosterone, dihydrotestosterone, and androstenedione were extracted from serum with ether and separated by celite chromatography before assay with specific single-antibody radioimmunoassays (21).

Statistical analyses

Demographic data are presented as means ± SD; the remainder of the data are expressed as means ± SE. Statistical

Table 1—*Demographic characteristics of the patients with (group 1) or without (group 2) a history of premenstrual hyperglycemia*

	GROUP 1	GROUP 2
NUMBER (N)	7	9
AGE (YR)	30 ± 3	28 ± 6
DIABETES DURATION (YR)	18 ± 7	18 ± 9
BODY MASS INDEX (KG/M^2)	24 ± 3	24 ± 4
INSULIN DOSE (U/DAY)	43 ± 10	38 ± 8
GLYCOHEMOGLOBIN (%)	10.4 ± 2.4	10.2 ± 2.5

Data are expressed as means ± SD.

comparisons between groups were performed using a two-way analysis of variance with repeated measures. Post hoc Student's *t* tests (paired or unpaired as appropriate) were performed when the analysis of variance indicated a significant group, treatment, or interaction effect. Pearson's correlation coefficient (*r*) was used to test for associations between variables.

RESULTS— There was no significant difference between the glucose levels at the start of the hyperglycemic clamp during the follicular and luteal phase studies (8.0 ± 0.3 vs. 7.7 ± 0.4 mM). During the final 60 min of the hyperglycemic clamp, the mean arterialized plasma glucose level was raised to 11.7 ± 0.1 mM during the follicular phase studies and 11.7 ± 0.1 mM during the luteal phase studies (NS). Plasma free insulin levels also did not differ significantly with basal levels of 16 ± 2 and 15 ± 1 mU/L and steady-state clamp levels of 23 ± 1 and 24 ± 4 mU/L for the follicular and luteal phase studies, respectively.

The characteristics of the subjects with (group 1) and without (group 2) premenstrual hyperglycemia are shown in Table 1. The groups did not differ significantly in age, diabetes duration, body mass index, total daily insulin dose, or glycosylated hemoglobin. The two groups of subjects also did not differ in the basal glucose or free insulin levels, or glucose and insulin levels attained during the final 60 min of the hyperglycemic clamp in either phase of the menstrual cycle.

Rates of glucose metabolism (M) are shown in Fig. 1. Group 1 subjects had a modest fall in glucose metabolism from the follicular to the luteal phase (30.2 ± 3.8 vs. 24.5 ± 2.0 $\mu mol \cdot kg^{-1} \cdot min^{-1}$, $P = 0.09$), whereas the rate increased in group 2 (18.5 ± 1.2 vs. 23.2 ± 2.3 $\mu mol \cdot kg^{-1} \cdot min^{-1}$, $P = 0.03$). A similar pattern was seen for insulin sensitivity expressed as the glucose metabolic rate divided by the steady-state plasma free insulin level (M-I ratio) (group 1 1.31 ± 0.18 vs. 1.02 ± 0.05, $P = 0.10$, group 2 0.87 ± 0.10 vs. 1.04 ± 0.14 $\mu mol \cdot kg^{-1} \cdot min^{-1}$ per mU/L, $P = 0.02$). The rates of glucose metabolism and insulin sensitivity were both significantly greater in group 1 than group 2 during the follicular phase ($P = 0.04$), whereas these values did not differ in the luteal phase (Fig. 1).

Sex steroid hormone levels appear in Table 2. Serum progesterone was significantly greater in the luteal phase in both groups of subjects, but levels did not differ significantly between the two groups in either menstrual cycle phase. In contrast, serum estradiol levels rose significantly from the follicular to the luteal phase in group 1 (164 ± 39 vs. 352 ± 59 pM, $P = 0.006$), whereas such a rise was not observed in group 2 (334 ± 156

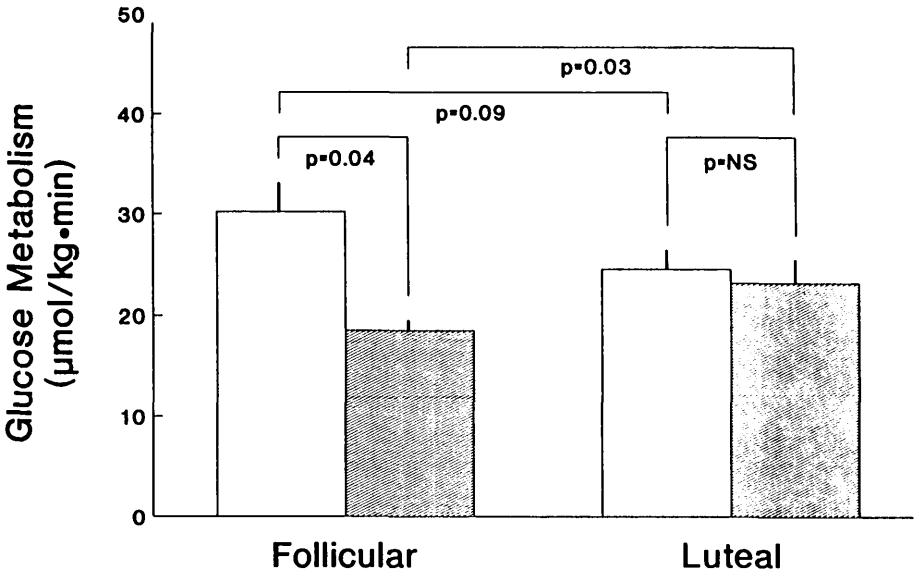

Figure 1—*Rates of glucose uptake in 7 patients with premenstrual hyperglycemia (group 1, open bars) and 9 patients without premenstrual hyperglycemia (group 2, shaded bars) during follicular and luteal phases of menstrual cycle. Data are expressed as means ± SE.*

Table 2—*Hormone levels during follicular and luteal phases of menstrual cycle in diabetic women with (group 1) or without (group 2) a history of premenstrual hyperglycemia*

	Group 1 (N = 7)		Group 2 (N = 9)	
	Follicular	Luteal	Follicular	Luteal
Progesterone (nM) Follicular: <6 Luteal: 8–80	0	43 ± 4*	0.4 ± 0.3	45 ± 9*
Estradiol (pM) Follicular: >50 Luteal: 200–600	164 ± 39	352 ± 59†	334 ± 156	423 ± 74
Follicular-stimulating hormone (IU/L) Follicular: 3–12 Luteal: 1–12	5.8 ± 0.4	2.3 ± 0.6†	5.6 ± 1.4	1.6 ± 0.7†
Luteinizing hormone (IU/L) Follicular: 2–13 Luteal: 1–19	3.1 ± 0.9	1.5 ± 0.6‡	4.4 ± 1.1	2.2 ± 0.3
Prolactin (pM) 120–1150	506 ± 155	435 ± 115	564 ± 129	586 ± 124
Testosterone (nM) 0.7–2.8	0.90 ± 0.13	1.07 ± 0.26	1.26 ± 0.13	1.39 ± 0.20
Dihydrotestosterone (nM) 0.1–0.8	0.35 ± 0.05	0.39 ± 0.05	0.46 ± 0.09	0.53 ± 0.07
Androstenedione (nM) 2.1–10.5	2.40 ± 0.70	2.84 ± 0.81	2.30 ± 0.66	2.67 ± 0.71

Data are expressed as means ± SE. Normal ranges are listed below each hormone.
*$P < 0.001$ vs. follicular phase.
†$P < 0.01$ vs. follicular phase.
‡$P < 0.05$ vs. follicular phase.

vs. 423 ± 74 pM, NS). Serum testosterone was slightly higher in group 2 than group 1 during the follicular phase (1.26 ± 0.13 vs. 0.90 ± 0.13 nM, $P = 0.08$). Levels of dihydrotestosterone and androstenedione did not differ between the groups of subjects or between the two phases of the menstrual cycle in either group. FSH, LH, and prolactin levels also did not differ between groups (Table 2).

When data from all subjects were combined, the change in glucose uptake between the follicular and luteal phase had a weak negative correlation with the change in estradiol levels between the two menstrual cycle phases ($r = -0.434$, $P = 0.09$). It is possible that with larger sample sizes, however, this relationship might have reached statistical significance. No correlation was found between glucose disposal and changes in levels of progesterone, testosterone, dihydrotestosterone, or androstenedione.

CONCLUSIONS— In this study, paired hyperglycemic clamps were performed in the midfollicular and midluteal phases in 16 women with established IDDM. In the group as a whole, there was no difference in average glucose disposal rate during the follicular and luteal phase studies. However, both the clinical histories of the subjects regarding the presence or absence of premenstrual hyperglycemia and the alterations in glucose metabolism throughout the menstrual cycle were heterogeneous. A subgroup of seven patients (group 1) with a history of premenstrual hyperglycemia and/or increase in insulin requirement was identified. In these subjects serum estradiol rose normally from the follicular to the luteal phase. A second subgroup (group 2) of nine subjects had no history of alterations in glucose homeostasis during the late luteal phase. In these patients serum estradiol levels were equally elevated during the follicular and luteal phase studies. Serum testosterone was slightly higher in group 2 than group 1 during the follicular phase. No differ-

ences were identified between these two subgroups in serum progesterone, gonadotropins, prolactin, dihydrotestosterone, or androstenedione in either phase of the cycle.

Previous investigators have used various techniques to evaluate glucose disposal throughout the menstrual cycle, although most studies have been performed in nondiabetic women. Roy, Ghosh, and Bhattacharjee (4) and Jarett and Graver (5) performed OGTTs in nondiabetic women at different phases of the menstrual cycle and found the best glucose tolerance occurred early in the follicular phase. In contrast, Bonora et al. (6) and Cudworth and Veevers (7), also using the OGTTs in healthy women, failed to identify such variation. Spellacy, Carlson, and Schade (8) used the intravenous glucose tolerance test in nondiabetic women and also failed to find variation associated with the menstrual cycle.

Two groups of investigators (9,10) studied follicular and luteal phase glucose metabolism in nondiabetic women with the euglycemic insulin clamp technique and neither found consistent alterations in glucose metabolism. However, both studies were performed at euglycemic levels in nondiabetic women, so the results may not be applicable to the hyperglycemic state that is characteristic of IDDM. We attempted to clarify the potential impact of hyperglycemia on glucose metabolism in the follicular and luteal phases in nondiabetic women using the hyperglycemic clamp technique (11). In contrast to previous studies that used the euglycemic clamp technique, a consistent decrease in insulin-mediated glucose uptake was observed from the follicular to the luteal phase (11). The women in our previous study had follicular and luteal phase estradiol levels that were comparable to the subgroup of our patients in whom glucose metabolism also declined from the follicular to the luteal phase. The differing results with the hyperglycemic versus euglycemic clamp techniques suggest that changes in glucose-mediated glucose uptake may be responsible for the observed alterations in carbohydrate metabolism (22). Consistent with this hypothesis is the fact that glucose-mediated glucose uptake has been shown to be impaired in non-insulin-dependent diabetes and other states of abnormal carbohydrate metabolism (14).

In contrast to these physiological measurements in nondiabetic women is the long-standing clinical impression that women with IDDM frequently experience a deterioration in glycemic control in the premenstrual period. As long ago as 1942, Cramer (1) reviewed the hospital records for 18 yr of all female diabetic patients between the ages of 14–45 yr admitted in ketoacidosis. Of the 36 women who were menstruating as part of their regular cycle and who had no obvious infectious precipitating cause for ketoacidosis, 17 (47%) were admitted within 2 days of the 1st day of their menstrual period. In a similar study, Walsh and Malins (2) found that 31 of 53 episodes of ketoacidosis in premenopausal women were associated with menstruation, whereas an incidence of 32% would be expected by chance alone. In addition, a survey of their female patients revealed that 38% perceived a change in diabetic control around the time of menstruation. In 27%, a deterioration in glycemic control was observed, whereas improvement was noted in 12%. These clinical findings are in agreement with the heterogeneity observed in our measured rates of glucose metabolism throughout the menstrual cycle in diabetic women.

Alterations in insulin receptor binding and affinity at different times during the menstrual cycle have been reported as a potential explanation for this phenomenon. De Pirro et al. (23) studied insulin binding to monocytes in eight regularly menstruating women and found a higher specific cell binding fraction during the follicular phase compared with the luteal phase, whereas studies in postmenopausal women and men failed to reveal significant variation over a 28-day period. Similar findings have been reported for insulin binding to erythrocytes (24,25). In contrast, Pedersen, Hjøllund, and Lindskov (26) failed to identify significant differences in insulin binding to adipose cells isolated from women in the follicular and luteal phases. This would suggest that postbinding defects may also contribute to the variability in glucose metabolism throughout the menstrual cycle.

Because hepatic glucose production (HGP) was not measured in this study, it is possible that changes in suppression of hepatic glucose output could have contributed to the observed differences in glucose disposal. The levels of free insulin achieved in our study (~25 mU/L) may not have been adequate to suppress endogenous glucose production in all subjects. However, Toth et al. (10) have previously examined the effects of insulin on HGP in the follicular, luteal, and menstrual phases in normal women under euglycemic conditions. No differences were found in basal hepatic glucose output, and full suppression of HGP was observed with an insulin infusion rate of 15 $mU \cdot m^{-2} \cdot min^{-1}$ in all menstrual cycle phases. Moreover, our study was performed under hyperglycemic conditions (11.7 mM) that would tend to further suppress endogenous glucose release (14). Thus, changes in hepatic glucose output are unlikely to play a major role in the alterations in glucose metabolism observed in this study.

Attempts to identify the specific hormone(s) responsible for menstrual cycle–associated changes in carbohydrate metabolism have also yielded various results. Older prospective studies of nondiabetic women placed on oral contraceptive agents have revealed an incidence of ~4% of diabetic oral or intravenous glucose tolerance tests (27). However, a more recent study

(28) in which the metabolic effects of seven low-dose oral contraceptives (30–40 μg ethinyl estradiol) were examined failed to show any significant differences in oral glucose tolerance. Spellacy et al. (29) examined the effects of estrogen alone on carbohydrate metabolism, as assessed by the oral glucose tolerance test. In the premenopausal women studied, little change or a slight improvement in glucose tolerance was observed, whereas increased glucose levels were observed in the postmenopausal women receiving estrogen preparations. In female monkeys Beck, Venable, and Hoff (30) found no significant change in glucose tolerance (with the intravenous glucose tolerance test) after 3 wk of treatment with ethinyl estradiol. Thus, physiological levels of estrogen or estrogenic analogues have generally been found to have minimal effects on carbohydrate metabolism in nondiabetic women (31). However, even small deleterious effects of estrogens on carbohydrate homeostasis may be exaggerated in the patient with IDDM in whom the normal feedback regulation between plasma glucose levels and insulin secretion is absent.

Progestational agents also appear to induce a variable degree of insulin resistance, which is determined by the dose and potency of the preparation administered (32,33). Several studies indicate that norgestrel may have greater adverse effects on glucose tolerance than other preparations (32,34–36). Finally, Beck, Venable, and Hoff (30) found no significant changes in intravenous glucose tolerance in monkeys with the administration of norethindrone, medroxyprogesterone acetate, mestranol, or ethinyl estradiol alone. However, concurrent administration of norethindrone with either estrogen preparation resulted in an increase in fasting insulin levels and the insulin response to glucose without a change in glycemic profile. Extrapolation of studies in which the metabolic effects of exogenous sex steroids on glucose metabolism are examined to the clinical situation in which endogenous steroids are acting may be problematic given the complex hormonal interplay that is evident during the menstrual cycle.

Recent work has focused on the association of insulin resistance with hyperinsulinemia and elevated androgen levels. Hyperinsulinemia and hyperandrogenemia are strongly correlated in women with polycystic ovarian disease (37,38). Although there is some evidence that hyperandrogenism can produce insulin resistance (39), elimination of the hyperandrogenism may not significantly improve insulin sensitivity in these women (40). In contrast, there are considerably stronger data to support the hypothesis that it is the hyperinsulinemia that results in ovarian hyperandrogenism and not the converse. For example, treatment of hyperandrogenic women with diazoxide to decrease basal and glucose-stimulated insulin levels results in a decrease in serum testosterone levels (41). Moreover, insulin is known to stimulate androgen production in cultured ovarian stroma and theca (42,43). Given these data, it is not surprising that in our subjects we were unable to identify a correlation between levels of androgens and insulin-stimulated glucose metabolism.

Finally, it should be noted that the data from our study cannot be used to establish a causal relationship between changes in glucose uptake and the presence of hyperglycemia during the late luteal phase, because sustained hyperglycemia itself may impair glucose uptake (44). Moreover, many other factors are known to affect insulin action in vivo, including other hormones (e.g., catecholamines, cortisol, growth hormone), substrates (e.g., free fatty acids, ketones), physical activity, and diet. Clearly, further studies are needed in which these variables are more rigorously controlled.

In summary, it is evident from our study and that of previous investigators that marked heterogeneity exists in the clinical observations and the metabolic measurements of glucose homeostasis in different phases of the menstrual cycle. We were able to identify a subgroup of diabetic women with a history of premenstrual hyperglycemia. In these same women, rates of glucose disposal, measured under hyperglycemic conditions, decreased from the follicular to the luteal phase. In contrast, a second group of women exhibited an increase in whole body glucose uptake in the late luteal phase. Future studies in which the hormonal milieu is altered in such women by the administration of various sex steroid hormones may help increase our understanding of the mechanisms underlying these changes and provide a rational basis for treatment of this phenomenon.

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