Short-term effects of a progestational contraceptive drug on food intake, resting energy expenditure, and body weight in young women[1–3]

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ABSTRACT
Background: Studies showed that hormonal fluctuations that occur over the human menstrual cycle affect energy intake and expenditure. However, little is known about the possible effects on body weight regulation that may arise when these cyclic changes are suppressed with hormonal contraceptives.
Objective: The aim of this study was to examine how a progestational contraceptive drug (depot medroxyprogesterone acetate) affects food intake, resting energy expenditure (REE), and body weight in young women.
Design: Twenty normal-weight women were tested in a single-blind, placebo-controlled experiment. Body weight, REE, and 3-d food intake (food provided) were measured in the follicular and luteal phases of 2 menstrual cycles before a single injection of depot medroxyprogesterone or saline solution was administered. Measurements were also taken 4 times after injection: in the luteal and follicular phases of 2 cycles in the placebo group and 2 wk apart (to mimic timing of the menstrual phases) in the drug group.
Results: Before injection, the phase of the menstrual cycle affected both energy intake and REE. The study participants consumed more energy (4.3%; $P = 0.02$) and expended more energy at rest (4.3%; $P = 0.0002$) in the luteal phase than in the follicular phase. Comparison of pre- and postinjection means showed that treatment with the contraceptive drug had no significant effects on energy intake, REE, or body weight.
Conclusions: This study showed that, although phases of the menstrual cycle affected energy intake and REE, depot medroxyprogesterone acetate did not alter energy intake or expenditure or cause weight gain in young women. *Am J Clin Nutr* 2001;73:19–26.

KEY WORDS Food intake, resting energy expenditure, menstrual cycle, depot medroxyprogesterone acetate, contraception, body weight

INTRODUCTION

Despite the extensive use of female contraceptive hormones worldwide, little is known about the effects of these hormones on the regulation of body weight. Drug manufacturers cite weight change as an adverse reaction for each of the 33 hormonal contraceptive drugs listed in the *Physicians' Desk Refer-* *ence* (1). However, for all but one of these drugs, the change in weight is described as a possible increase or decrease. Only for Norplant (Wyeth-Ayerst Laboratories, St Davids, PA) is there a specific statement that the expected change is an increase in body weight. Published studies on the effects of oral contraceptives showed that long-term use is not associated with increases in weight (2, 3). Despite these findings, it is a common perception among women that oral and other hormonal contraceptives cause weight gain. Preliminary reports suggest that these perceptions may be justified for some newer contraceptive drugs. Implanted (Norplant) and injected (Depo-Provera; Upjohn and Pharmacia, Inc, Kalamazoo, MI) forms of progestin were found to lead to increases in appetite and body weight (4, 5). In 1995, more than one million American women used Depo-Provera and >500000 used Norplant (6). Clearly, it is important to determine whether the use of these drugs can be expected to promote weight gain in women.

The mechanisms by which contraceptive hormones may affect body weight are not known. Numerous studies showed that energy intake and expenditure are altered across phases of the menstrual cycle (7–16). Few researchers examined how these cyclic changes are affected when ovulation is suppressed by a contraceptive drug (17, 18). The purpose of this study was to determine whether the use of a progestational contraceptive causes an imbalance in energy regulation that leads to weight gain. Specifically, we examined whether depot medroxyprogesterone acetate was associated with an increase in food intake or a decrease in resting energy expenditure (REE) in young women.
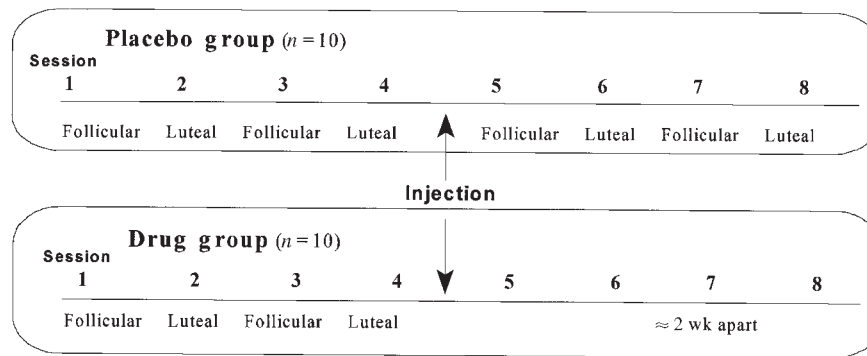
FIGURE 1. Test schedule across the follicular and luteal phases of the menstrual cycle before and after injection with depot medroxyprogesterone acetate or placebo.

SUBJECTS AND METHODS

Subjects

We recruited participants through advertisements posted on campus and in the campus newspaper. Potential subjects, who were female and aged 20–35 y, were screened initially by telephone to ensure that they had regular menstrual cycles, had not used contraceptive hormones in the previous year, had no food restrictions, were nonsmokers, were not currently taking medications known to affect appetite, were not lactating or pregnant (or planning to become pregnant in the next 15 mo), and were willing to be randomly assigned to receive one injection of depot medroxyprogesterone acetate or saline. The subjects were then scheduled to visit the laboratory for measurement of height and weight and to complete the following questionnaires: a demographic and health-history questionnaire; the Zung Self-Rating Depression Scale (19; possible score: 20–80) and the Beck Depression Inventory (20; possible score: 0–63), both of which detect depression; the Eating Attitudes Test (21; possible score: 0–140), which detects symptoms of an eating disorder; the Eating Inventory (22), which measures dietary restraint (possible score: 0–21), perceived hunger (possible score: 0–14), and disinhibition (possible score: 0–16); the Eating Self-Efficacy Scale (23), which measures the ability to control food intake in response to social influences (possible score: 10–70) and negative affect (possible score: 10–160); and the Binge Eating Scale (24; possible score: 0–48). Potential subjects were excluded if they scored ≥40 on the Zung scale, ≥10 on the Beck Depression Inventory, ≥30 on the Eating Attitudes Test, or >10 on the restraint scale of the Eating Inventory.

All aspects of the study were approved by the Institutional Review Board of The Pennsylvania State University. The subjects signed and received copies of 3 consent forms: the first for administration of the screening questionnaire, the second for admission to the study, and the third to receive the injection of saline solution or depot medroxyprogesterone acetate. The subjects were informed (in the initial screening telephone interview and in the study consent form) that they would be randomly assigned to receive one injection of depot medroxyprogesterone acetate or saline solution. The subjects were also given the manufacturer's booklet describing the potential adverse effects of depot medroxyprogesterone acetate before they signed the study consent form.

Study design

This study used a randomized pre-post design (**Figure 1**). The subjects were randomly assigned to receive one injection of depot medroxyprogesterone acetate (Depo-Provera) or saline solution and were tested during pre- and postinjection intervals. To assess the effects of the menstrual phase on the variables of interest, sessions were scheduled to occur during ≥2 follicular and 2 luteal phases in the preinjection interval. To ensure that order effects did not systematically bias the results, half of the participants in each group started the study in the luteal phase of the menstrual cycle and half started in the follicular phase. To reduce intercycle variability, the women were tested in the follicular and luteal phases of the same cycle whenever possible. In the postinjection interval, the women were tested 4 more times. Women who received saline solution were tested during 2 follicular and 2 luteal phases after injection, whereas women who received the contraceptive drug were no longer cycling and were tested at 2-wk intervals to mimic the timing of the menstrual cycle phases.

Procedures

The women admitted to the study attended a 1-h training session before testing began to review all study procedures. The subjects were placed under a metabolic hood for 10 min to acclimate them with this procedure (25). They were also shown how to record their menstrual cycles (on forms provided) and use ovulation-detection test strips (OvuQuick OS; Quidel Corporation, San Diego). Subjects who completed the training session were screened by staff at the Women's Health Department of Penn State University Health Services for possible contraindications for use of Depo-Provera; the same standardized screening procedures were used as those used for clinic patients. Depo-Provera is an aqueous suspension of depot medroxyprogesterone acetate (150 mg) that is injected into muscle tissue and released slowly over time. The circulating depot medroxyprogesterone acetate inhibits ovulation for ≥3 mo by suppressing the midcycle rise in luteinizing hormone and follicle-stimulating hormone (26). In the current study, injections were given in the gluteal muscle while the subjects faced away from the nurse so that they would not see the syringes containing the drug, which is a creamy white liquid, or the saline solution, which is a colorless liquid.

Test sessions

In each test session, the subjects reported to the laboratory for 4 consecutive days. On days 1, 2, and 3, the subjects consumed only foods and beverages (including water) that were provided by the laboratory. The subjects were asked to choose additional food items, from an extensive list of beverages and snack items, in

TABLE 1
Three-day menu served during each test session[1]

Meal	Day 1	Day 2	Day 3
Breakfast	Cinnamon-raisin bagel with choice of full-fat or reduced-fat cream cheese plus choice of 4 breakfast cereals	Honey-wheat English muffin with jam plus choice of 4 breakfast cereals	Croissant with jam plus choice of 4 breakfast cereals
Lunch	Whole-wheat sliced bread, ham slices, cheese slices, and lettuce	Plain bagel with choice of full-fat or reduced-fat cream cheese	Kaiser roll, turkey slices, cheese slices, and lettuce
Dinner	Turkey and stuffing, gravy, mashed potatoes, and peas	Vegetable and cheese lasagna, tossed salad with choice of dressings, Italian bread, and butter	Chicken burritos, Spanish rice, refried beans, corn, salsa, cheese, sour cream, and chopped tomatoes

[1] In addition to these foods, the subjects chose beverages and snacks from an extensive list of commonly available packaged products and fresh foods. Details of the foods and serving sizes offered are available from the authors on request.

addition to the foods provided at each meal (**Table 1**). The list of optional foods included commonly available packaged snack foods (eg, potato chips, pretzels, and chocolate bars), dairy products (eg, yogurt, milk, and pudding), and fresh fruit and vegetables. The wide choice of foods offered during meals and as snacks enabled the subjects to alter their energy and macronutrient intakes because the foods contained various amounts of fat, protein, and carbohydrate. On the morning of the first and fourth days, the subjects were weighed in street clothing, without shoes, before breakfast. On the fourth day, the subjects completed a taste test to assess hedonic and sensory responses to milk and sugar solutions and chocolate stimuli (results not reported).

The subjects consumed breakfast and dinner in the laboratory in individual cubicles. Lunch and evening snacks were packed in personal coolers to be taken out. Food items were weighed before and after the meals were served to determine the amount consumed to the nearest 0.1 g. For the take-out meals and snacks, food items were weighed before the coolers were packed and leftovers were weighed immediately when the coolers were returned at the next meal. Energy and macronutrient consumption was calculated by using the nutritional information provided by the manufacturer or from Bowes and Church (27) for nonlabeled items (eg, fresh produce).

Session scheduling

Scheduling of the sessions was based on each woman's menstrual cycle. The subjects were instructed to contact the experimenter at the beginning of each new cycle (ie, the onset of menstruation) or when a positive result was detected with the ovulation test strips. The subjects were asked to bring completed urine strips to the laboratory as soon as possible to allow the investigator to confirm the positive reading. Follicular-phase sessions were scheduled to begin 3–5 d before the estimated ovulation date and luteal-phase sessions were scheduled to begin 6–10 d after a positive ovulation test to coincide with peak estrogen and progesterone concentrations associated with these phases.

Resting energy expenditure

REE was measured before breakfast (after a 12-h fast) on the first day of each test session. Metabolic tests were performed in a temperature-controlled room with a Deltatrac II indirect calorimeter (SensorMedics Corporation, Yorba Linda, CA) by using a standard protocol. For the first 20 min, the subjects lay on a bed and were permitted to read. Body temperature was taken with an instant thermometer (Thermoscan Incorporated, San Diego) during the last 5 min of the rest period to ensure absence

of fever. The metabolic hood was then placed over the subject's head for 40 min; readings were suppressed for the first 10 min. Staff were present during the 1-h test interval to ensure that the subjects were not sleeping. The Deltatrac monitor was calibrated before each test with use of oxygen–carbon dioxide (95:5, by vol) gas supplied by the manufacturer. Airflow calibration was performed at 3-mo intervals during the course of the study by using the ethanol-burning apparatus supplied with the calorimeter.

Blinding procedures and debriefing

Double-blinding procedures were used whenever possible such that the personnel who conducted most of the test procedures (serving meals, conducting metabolic and taste tests, or taking anthropometric measurements) were unaware of the treatment or menstrual cycle status of the subjects. However, the lead investigator participated in subject testing and was aware of the subjects' group assignments and menstrual phase statuses, as was the supervising nurse who coordinated the injections.

Although the subjects had been informed in the consent forms of all procedures to be used in the experiment, precautions were taken to prevent the subjects from recognizing that testing was being done during specific phases of their menstrual cycles; this was because previous studies showed that research results can be affected by expectancies and attributions associated with testing over menstrual phases (28, 29). Thus, the subjects were not told the purpose of the ovulation test strips. The identifying product names were obliterated from the strips before they were given to the subjects. The subjects were told by the lead investigator when to perform the tests but were not told what the results of the tests indicated. To provide a blind for tracking and recording their menstrual cycles, the subjects were told that the metabolic tests could not be performed during menstruation.

At the end of the study, the subjects completed a discharge questionnaire consisting of open-ended questions assessing their perceptions of the general purpose of the experiment and the purpose of specific procedures used during the study. The investigator reviewed the questionnaire with each subject to elaborate on her answers and to address further questions. The subjects were asked to guess whether they had received the drug or the saline solution and to indicate how sure they were of their guesses on a visual-analogue scale (100 mm) anchored by the phrases "not at all sure" and "extremely sure."

Data analyses

Data were analyzed with use of SAS-PC for WINDOWS (version 7.0; SAS Institute Inc, Cary, NC). Results were considered

TABLE 2
Baseline characteristics of the study participants by treatment group[1]

	Placebo group (n = 10)	Drug group (n = 10)
Age (y)	23.7 ± 1.3 (21–34)	22.7 ± 0.9 (20–29)
Weight (kg)	58.9 ± 2.6 (48.6–72.5)	59.8 ± 1.7 (49.8–65.7)
BMI (kg/m^2)	21.9 ± 0.8 (19.0–26.7)	21.3 ± 0.6 (18.4–24.0)
Zung Self-Rating Depression Scale	26.6 ± 0.9 (23–32)	28.6 ± 1.5 (23–37)
Beck Depression Inventory	1.7 ± 1.0 (0–10)	2.1 ± 0.4 (0–4)
Eating Attitudes Test	5.9 ± 1.1 (2–13)	5.6 ± 1.1 (2–12)
Eating Inventory—Cognitive Restraint	3.8 ± 0.7 (0–7)	5.6 ± 1.3 (0–10)
Eating Inventory—Disinhibition	3.4 ± 0.7 (0–7)	2.6 ± 0.4 (1–5)
Eating Inventory—Hunger	3.6 ± 0.6 (1–6)	3.4 ± 0.8 (0–8)
Eating Self-Efficacy Scale—Affect	24.9 ± 2.7 (16–40)	32.2 ± 4.6 (18–62)
Eating Self-Efficacy Scale—Social	27.7 ± 4.0 (10–50)	23.3 ± 2.4 (14–39)
Binge Eating Scale	3.6 ± 1.0 (0–10)	2.6 ± 0.9 (0–8)

[1] $\overline{x}$ ± SEM; range in parentheses.

significant at $P < 0.05$. Baseline characteristics of the participants were analyzed between groups by using a t test, adjusted for unequal variance, as appropriate. In the models described below, the mixed procedure of SAS-PC (PROC MIXED) was used to test for effects of menstrual phase and treatment. For each model, the data were first examined for the presence of outliers and for normality and equality of variance by using a univariate procedure. The influence of each observation on the regression function was examined by using DFFITS (an approximation of the number of SDs that a fitted value changes when a particular observation is removed from the data set). Observations with $P < 0.001$ for the Studentized residual and |DFITTS|>2 were considered to be significant outliers. The reported data are least-squares means (±SEMs) from the mixed models.

Effects of menstrual phase

To test the effects of menstrual phase on REE, only pretreatment data were used and phase, group, and group × phase terms were entered into the mixed model. For food intake and body weight, the effects of day were added to the model. One observation was found to be a significant outlier in the model that tested the effects of menstrual phase on REE (DFITTS = 4.2, Studentized residual = 6.9) and was deleted from the analyses.

Effects of treatment

To test the effects of treatment with depot medroxyprogesterone acetate on intake, body weight, and REE, the data were collapsed across phase and the posttreatment data were used; the preinjection data were entered as covariates in each model. Use of this approach made it possible to test the effects of treatment on the variables of interest with each person acting as her own control (30).

Further analyses were conducted to examine whether any changes in body weight occurred over time that may have been obscured in pre- and posttreatment comparisons. Specifically, we compared body weight at the final preinjection time point with measures taken at the last 4 time points after injection. PROC MIXED was used to test for effects of group and time and the interaction of group and time.

Analyses were also conducted to explore how the cyclic changes in REE were affected by treatment with depot medroxyprogesterone acetate. Some authors have speculated that suppression of ovulation with contraceptives will prevent the increase in REE seen in the luteal phase of normal cycles and thereby cause weight gain (31). Alternatively, the findings of Eck et al (17) sug-

gest that suppression of the cycle prevents the normal decrease in the follicular phase of the cycle, with the net result that weight loss is favored. We could test these competing hypotheses in the current study by using contrast statements to compare the postinjection mean with the preinjection follicular and luteal phase means.

Power analyses

Initial sample size estimates were made on the basis of previously published studies that compared the follicular and luteal phases of the menstrual cycle for food intake (14, 32) and REE (8, 9, 11). We determined that a sample of 20 (with repeated measures across 2 menstrual cycles) would be adequate to enable detection of the effects of menstrual phase. However, we anticipated that the statistical power of the design to detect differential changes between groups (depot medroxyprogesterone acetate compared with placebo) would be less than the power to detect effects of menstrual phase because of the higher error variance involved in between-group comparisons than in within-group comparisons. However, because each person's preinjection measurement could serve as its own control, we concluded that the error variance would be less than in the between-group design. Because we did not have access to published data to estimate this variance and because sample size was limited by practical constraints (related to the complexity of the testing protocol involved for each subject), we used post hoc analyses of the data to determine the statistical power of the design to detect effects of treatment. Specifically, changes in food intake, REE, and body weight were computed for each individual, and means and SDs for each change score were then computed by treatment group. These data were used to determine the minimum differential change that could be detected between groups with power set to 0.80 and α set to 0.05.

RESULTS

Twenty-four women were admitted to the study. Four women were excluded before they received injections because of irregularity of their menstrual cycles (n = 3) or failure to confirm ovulation in 3 consecutive menstrual cycles (n = 1). Thus, the final sample consisted of 20 women (10 in each group). There were no significant differences in baseline characteristics between groups (**Table 2**). Nineteen of the subjects were nulliparous. Seventy percent were classified as non-Hispanic white, 5% as Asian or Pacific Islander, 10% as Hispanic, and 15% as non-Hispanic black.
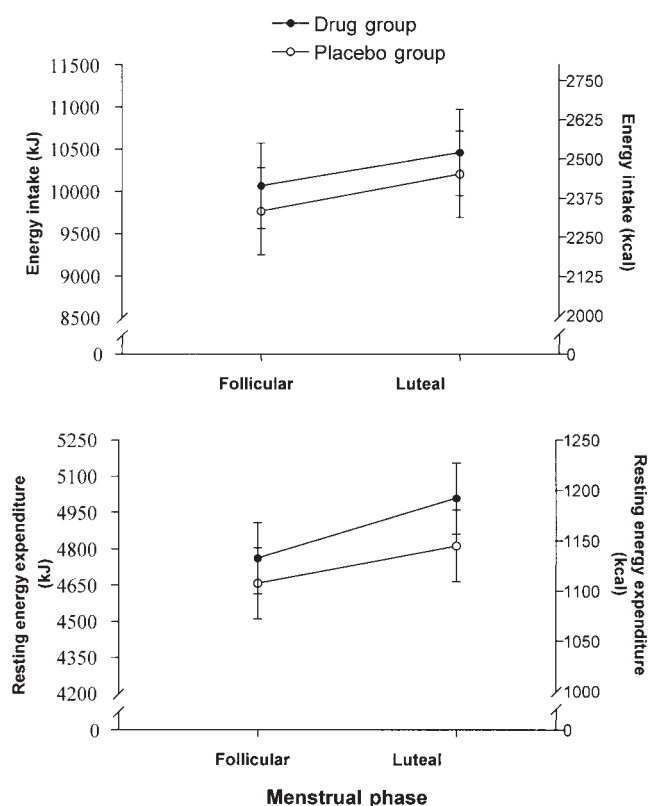
FIGURE 2. Least-squares mean (±SEM) daily energy intake (top) and resting metabolic rate (bottom) in the follicular and luteal phases of the menstrual cycle before injection with depot medroxyprogesterone or placebo ($n = 10$ per group).

Results from 171 test sessions were used in the data analyses. All subjects completed ≥8 test sessions (Figure 1). In some cases subjects were scheduled for additional sessions so that data could be collected during the follicular and luteal phases of the same cycle whenever possible. Excluding the 40 postinjection sessions in the drug group, 79% of the sessions were preceded or followed by a positive ovulation test result.

Effects of menstrual phase

Results of the mixed-model analyses of the preinjection data showed a significant main effect of menstrual phase on energy intake ($P = 0.021$) and REE ($P = 0.0002$) (**Figure 2**). The subjects consumed 4.3% more energy (423 kJ/d) and expended 4.3% more energy at rest (201 kJ/d) in the luteal phase than in the follicular phase of the menstrual cycle. Body weight was also affected by menstrual phase (luteal phase, 59.5 ± 1.5 kg; follicular phase, 59.2 ± 1.5 kg; $P = 0.002$).

There were no significant differences between groups and no interactions of phase and group for energy intake, body weight, or REE. The results were unaffected by the exclusion of sessions in which ovulation was not confirmed or the follicular and luteal phases were not in the same cycle.

Menstrual phase significantly affected the total daily weight of food, beverages, and macronutrients consumed (**Table 3**). The subjects ate 5.1% more food and drank 9.8% less water and other non-energy-containing beverages during the luteal phase than in the follicular phase of the menstrual cycle. The percentage of

energy for each macronutrient consumed was constant across menstrual phases.

The design of this study provided a unique opportunity to examine whether changes in energy intake, body weight, and energy expenditure were correlated across menstrual phases. To test this hypothesis, data were used from sessions in which testing in the follicular and luteal phases occurred within the same cycle. One hundred two sessions (representing 51 complete menstrual cycles) were included in the analyses. Pearson correlation coefficients were calculated to examine the relation between the change in body weight and the percentage change in energy intake and REE. The results showed that change in body weight was correlated with change in energy intake ($r = 0.28$, $P = 0.048$) but not REE ($r = 0.06$, $P = 0.67$). Although the changes in energy intake and REE were of the same magnitude (4.3%), they were not significantly correlated ($r = 0.058$, $P = 0.69$).

Effects of treatment

Treatment with depot medroxyprogesterone acetate had no significant effect on food intake, body weight, or REE (**Table 4**). Comparisons of the pre- and posttreatment intervals showed that both groups ate less after treatment; however, the change was not significantly different between groups.

No significant differences in change in body weight over time were found between groups (**Figure 3**). Comparing the effects of time within each group, we found that the only significant difference was that women in the placebo group weighed more at the last time point (59.0 g ± 2.1 kg) than at the preinjection time point (58.3 ± 2.1 kg; $P = 0.023$).

For women who received depot medroxyprogesterone acetate, REE after injection (4912 kJ/d) was significantly higher than that during the follicular-phase sessions before injection (4761 kJ/d; $P = 0.01$) but not significantly different from that during the luteal-phase sessions before injection (5008 kJ/d; $P = 0.12$).

Debriefing

All subjects reported that they thought the purpose of the experiment was to examine the effects of Depo-Provera (or reproductive hormones) on some aspect of feeding behavior or energy metabolism. This belief was expected because it was consistent with the general purpose that was stated on the consent forms. Only 3 subjects guessed that another purpose of the study was to examine changes over the menstrual cycle. When asked to

TABLE 3
Energy intake and weight and macronutrient compositions of foods consumed across phases of the menstrual cycle before treatment[1]

	Follicular phase	Luteal phase	P
Energy intake (kJ)	9924 ± 368[1]	10330 ± 368	0.021
Food and beverage intake (g)[2]	2006 ± 120	2108 ± 120	0.016
Non-energy-containing beverage intake (g)[3]	1209 ± 173	1090 ± 173	0.033
Fat intake (g)	71.1 ± 3.5	75.1 ± 3.5	0.046
Fat intake (% of energy)	26.8 ± 0.9	27.1 ± 0.9	0.41
Carbohydrate intake (g)	363.4 ± 14.2	378.5 ± 14.2	0.039
Carbohydrate intake (% of energy)	61.4 ± 1.0	61.2 ± 1.0	0.68
Protein intake (g)	69.9 ± 3.3	71.8 ± 3.3	0.14
Protein intake (% of energy)	11.9 ± 0.4	11.7 ± 0.4	0.29

[1] Least-squares $\bar{x}$ ± SEM.
[2] Excludes water and non-energy-containing beverages.
[3] Includes water.

TABLE 4
Effects of treatment on food intake and resting energy expenditure

	Drug group		Placebo group		
	Pretreatment	Posttreatment	Pretreatment	Posttreatment	P^2
Food intake (kJ)	10263 ± 490[1]	10000 ± 490	9987 ± 490	9431 ± 490	0.37
Food and beverage intake (g)[3]	2108 ± 167	2031 ± 167	2006 ± 167	1884 ± 167	0.60
Non-energy-containing beverage intake (g)[4]	1352 ± 241	1299 ± 242	948 ± 241	912 ± 242	0.48
Fat intake (g)	69.6 ± 4.8	69.2 ±4.8	76.5 ± 4.8	72.9 ± 4.8	0.81
Fat intake (% of energy)	25.2 ±1.3	25.8 ± 1.3	28.7 ± 1.3	29.1 ± 1.3	0.35
Carbohydrate intake (g)	386.2 ± 19.5	372.2 ± 19.6	355.7 ± 19.5	336.6 ± 19.6	0.44
Carbohydrate intake (% of energy)	62.9 ± 1.3	62.2 ± 1.3	59.6 ± 1.3	59.2 ± 1.3	0.51
Protein intake (g)	72.2 ± 4.5	70.8 ± 4.5	69.6 ± 4.5	65.7 ± 4.5	0.24
Protein intake (% of energy)	11.9 ± 0.5	11.9 ± 0.6	11.7 ± 0.5	11.7 ± 0.6	0.81
Resting energy expenditure (kJ/d)	4883 ± 144	4912 ± 144	4732 ± 144	4736 ± 144	0.76
Body weight (kg)	59.9 ± 2.1	59.8 ± 2.1	58.8 ± 2.1	59.5 ± 2.1	0.13

[1] Least-squares $\bar{x}$ ± SEM.

[2] The P value refers to the effect of group when the pretreatment variable was used as a covariate.

[3] Excludes water and non-energy-containing beverages.

[4] Includes water.

provide further details, none of these 3 women stated explicitly that the luteal and follicular phases of the cycle were being examined. Half of the participants (5 in each group) stated correctly that the urine strips were used to detect ovulation, but none were aware of why the strips were used. All subjects in the drug group guessed that they had received Depo-Provera; they all reported changes in their menstrual cycles, such as prolonged bleeding. Two subjects in the placebo group guessed that they had received the drug. Results of a t test showed a trend for a between-group difference in the ratings of how sure subjects were about their guesses (drug group, 78 ± 8 mm; placebo group, 52.3 ± 11 mm; $P = 0.08$).

Power analyses

The results show that the sample size of 20 was adequate to test for effects of menstrual phase on the variables of interest. Because the experiment involved repeated measures, the precision for detecting relatively small effects of menstrual phase was enhanced by the exclusion of between-subject variability from the error term (33). This is evidenced in the results showing that even small changes in energy intake, REE, and body weight across menstrual phases could be detected.

In the data analyses for between-group comparisons, with power set to 0.80 and α set to 0.05, the following differential changes could be detected: 1.2 kg (1.9%) for body weight, 259 kJ/d (5.3%) for REE, and 1163 kJ/d (11%) for energy intake. Thus, the design of the present study had adequate power to detect a differential change of 1.2 kg in body weight between the depot medroxyprogesterone acetate and placebo groups over a 3-mo interval. This difference is equivalent to a differential change of 0.1 kg body wt/wk, which is the amount of change that would occur from an energy surfeit of only 439 kJ/d (4.4%). These results strengthen the conclusion that the sample size in the present study was sufficient to enable detection of a clinically significant effect of depot medroxyprogesterone acetate treatment on body weight if it existed.

DISCUSSION

This placebo-controlled experiment showed that depot medroxyprogesterone acetate did not cause weight gain in normal-weight young women over a 3-mo period. Comparing pre- with postinjection intervals, we found that mean body weight was 0.1 kg lower in the drug group and 0.7 kg higher in the placebo group. Our findings are consistent with those from longer-term clinical investigations that showed no effects of depot medroxyprogesterone acetate or other hormonal contraceptive drugs on body weight. Results from a retrospective review of patients' charts showed that women who used Depo-Provera ($n = 50$), Norplant ($n = 51$), or oral contraception ($n = 50$) for 1 y did not gain weight (34). Mean weight changes were 0.06, −1.6, and −0.9 kg, respectively, in the 3 groups. Similar results were found in studies of weight change in users of oral contraceptive hormones. In one study, 128 triphasic pill users recorded their body weights each day for 4 cycles. The mean change in weight from baseline to the end of the study was 0.0 kg (3). In a large study in Germany, weight change was investigated in 4746 adolescent users of a low-dose, monophasic oral contraceptive drug over a 6-mo interval. Most of the women (91.2%) either lost weight or had no weight change (2).
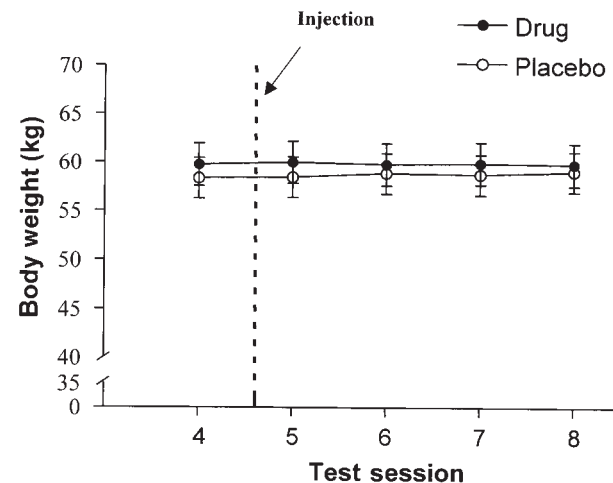

FIGURE 3. Least-squares mean (±SEM) body weight before injection (session 4) and at the last 4 time points after injection (sessions 5–8) with depot medroxyprogesterone acetate or placebo ($n = 10$ per group).

In this placebo-controlled study we prospectively examined changes in food intake and REE in the same women before and after contraceptive drug use. The results are consistent with those of other studies that found no effects of contraceptive drug use on energy intake but are inconsistent with respect to effects on energy metabolism. In 2 previous studies, groups of oral contraceptive pill users and nonusers were compared to assess differences in energy intake (17) and REE (17, 35). In the first study, REE and food-intake measurements (3-d diet records) were taken across 4 menstrual phases (menses, follicular phase, ovulation phase, and luteal phase). There were no significant between-group differences in energy intake or REE (17). In contrast, the second study showed a significant difference in REE between groups. Pill users were found to have a 5% higher REE than non-pill users after correction for differences in body weight (35). Opposite results for REE were found in a prospective study that compared measurements in 5 women over one menstrual cycle with measurements taken over a subsequent cycle in which the same women used an oral contraceptive drug. A 12% decline in REE was found when the pill and non-pill cycles were compared (18).

The conflicting results regarding the effect of contraceptive drugs on REE may be due in part to the timing of data collection over menstrual phases in noncontraceptive cycles. In the current study, the average of REE across menstrual phases and the comparison of pre- and postinjection measurements showed no significant effects of the drug. However, differences were found when postinjection measurements were compared with phase-specific preinjection measurements. Specifically, REE postinjection was <3% higher than during preinjection follicular phases and 2% lower than during luteal preinjection phases. Therefore, it is plausible that differences in the timing of measurement over the cycle accounted for differences in the results noted between studies. In the study that showed a significant decline in REE (18), REE measurements were taken weekly, 4 times both before and after pill use. In the study that compared pill users and nonusers (35), REE was measured only once but no information was given concerning timing. For each of these studies, it is not possible to ascertain the effect of the menstrual cycle on the measurements of REE taken during noncontraceptive cycles. Future studies must consider that REE may be underestimated if measurements are taken during follicular phases and overestimated if taken during the luteal phase.

The results of this study are consistent with those of other studies that showed increased food intake and REE in the luteal phase of the menstrual cycle (7–16). Estimates of the magnitude of the effect on energy intake range between 3.9% and 37%. Excluding the one extreme (7), most studies showed increases ranging from 4% to 16%. In the current study, the women consumed 4.3% more energy in the luteal phase than in the follicular phase. This result is consistent with findings from 2 previous studies in which all foods were provided. In one study, ad libitum intake of weighed experimental diets was compared for 10-d intervals before and after ovulation in 23 women. Energy intake was found to be 3.9% higher after ovulation than before ovulation (10). In the other study, the intakes of 9 women living in a metabolic ward for 52 d was compared over one menstrual cycle. Although energy intake was 6% higher in the luteal phase, the result was not significant, probably because the sample was small (36).

Our finding that REE increased by 4.3% in the luteal phase is also consistent with previous reports. In studies in which similar methods were used, estimates of the luteal rise in REE range

from 1.5% (16) to 9.5% (13). One study, in which an identical measurement protocol was used, showed no increase in REE during the luteal phase (37). The date of ovulation was not confirmed in that study. Rather, a simple counting method (from the date of menstruation) was used to define menstrual phases. Several investigators relied on this simple technique for designating phases of the menstrual cycle. In the current investigation we found that, in 20 women who were tested repeatedly over numerous cycles, only a few had typical 28-d cycles in which ovulation occurred close to day 14. For ovulatory cycles, the mean ovulation day was 15.4 and the mean cycle length was 29.5 d. However, these means obscure the variability that exists both between and within individuals. In cycles with positive ovulation results, the day of ovulation ranged from day 10 to day 20 and cycle lengths ranged from 21 to 39 d. The length of the luteal phase ranged from 10 to 23 d. Use of counting methods based on a standard 28-d cycle is likely to increase error variance. This may be an important consideration when adequate statistical power is needed to detect small changes over menstrual phases.

In conclusion, this placebo-controlled experiment showed that, although phase of the menstrual cycle affected both energy intake and REE, suppression of the cycle with depot medroxyprogesterone acetate did not cause short-term changes in energy intake or expenditure, or cause weight gain, in young healthy women. Further research is needed to determine whether similar effects occur with different contraceptive hormones, over longer periods of time, and in other populations, such as overweight or obese women.

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