Differences in macronutrient selections in users and nonusers of an oral contraceptive\textsuperscript{1-3}

Linda H Eck, A Gayle Bennett, Beth M Egan, JoAnne White Ray, Carol O Mitchell, Mary Ann Smith, and Robert C Klesges

ABSTRACT One of the problems inherent in using women in clinical research is the effect that oral contraceptive (OC) use might have on physical indexes. Although weight gain is frequently reported as a side effect of OC use, there is little empirical evidence that such weight gain actually occurs. The current study investigated differences in energy balance [i.e., dietary intake, resting energy expenditure (REE), and physical activity] between groups of users and nonusers of OCs. Each group completed a protocol that covered one menstrual cycle and consisted of daily recording of dietary intake, measurement of REE once during each phase of the menstrual cycle, and reporting of physical activity over the entire cycle. Comparisons indicate that there was a marginal interaction ($P = 0.06$) of OC use with total energy intake, indicating a different pattern of intake for the two groups. There were qualitative between-group differences such that the OC group consumed a greater percentage of energy as fat ($P = 0.02$) and a lesser percentage of energy as carbohydrate ($P = 0.008$). No group differences were found in the percentage of energy consumed as protein, but both groups consumed significantly less protein during menses ($P = 0.008$). There were no significant differences in REE. Both groups of women reported marginally more activity ($P = 0.09$) during menses than during the luteal phase. \textit{Am J Clin Nutr} 1997;65:419-24.

KEY WORDS Oral contraceptives, energy balance, weight gain

INTRODUCTION

Oral contraceptive pills (OCs) were first introduced in 1960. In the United States, it appears that OC use peaked at $\approx 68$ million users in 1973 \textsuperscript{(1)} and has remained between 50 and 60 million since the early 1980s \textsuperscript{(1)}.

One of the problems inherent in using women in clinical research is the effect that OC use might have on physical indexes. Alterations in energy balance are suspected because weight gain is frequently reported as a side effect of OC use \textsuperscript{(2)}. A few studies have reported anecdotal weight changes associated with OCs \textsuperscript{(2, 3)}, but this phenomenon has not been tested empirically. In the one investigation that directly studied weight \textsuperscript{(4)}, women ($n = 4$) consuming a constant amount of energy did not gain weight when an OC was introduced. This study and those that indirectly measured weight gain are largely inconclusive, but there remains a general belief that there is a relation between OC use and weight gain.

Although the connection between OCs and body weight has not been tested empirically, investigators conducting research on energy balance (i.e., dietary intake, metabolic rate, physical activity) routinely exclude women who are currently using OCs \textsuperscript{(5-9)}. This practice is both expensive because it increases the number of potential subjects that must be screened, and scientifically problematic because of issues of generalizability.

Only cursory attention has been given to studies regarding the effect of OCs on components of energy balance. To date, two studies have examined dietary differences between users and nonusers of OCs \textsuperscript{(10, 11)}. Whereas one study \textsuperscript{(10)} found that energy intake was significantly higher in OC users and macronutrient intake was similar in the two groups, the other study \textsuperscript{(11)} found no differences in energy intake between one nonpill cycle and one pill cycle.

The effect of OC use on energy expenditure (EE) has also received little attention. One study \textsuperscript{(12)} found that OC users showed no change from pre- to postovulation whereas non-OC users increased their 24-h EE between the two phases. One OC user that was followed for an additional month when she discontinued the OC also showed an increase in EE between the two phases, similar to that in the non-OC users the previous month. These findings appear to indicate a relation between OC use and a blunting of the expected rise in EE during the postovulatory phase.

Another study by McNeill et al \textsuperscript{(11)} concluded that the tendency of OC users to gain weight might be caused by a decline in basal metabolic rate (BMR) in response to the progestosterone in the OC. Subjects ($n = 5$) were followed during a no-pill cycle and a pill cycle. During each cycle, two measurements of BMR were made during the pre- and postovulatory phases, and energy intake and physical activity were estimated. Findings showed that when the women used the

\textsuperscript{1} From the Universities Prevention Center and the Department of Consumer Sciences, The University of Memphis.

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\textsuperscript{3} Address reprint requests to LH Eck, Universities Prevention Center, Psychology Department, Room 310, University of Memphis, Memphis, TN 38152. E-mail: Leck@mail.psyc.memphis.edu.

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OCs, they had a significant drop in BMR, whereas changes in energy intake and physical activity were not significant. It is not clear whether the drop in BMR occurred over the entire testing period or only during the postovulatory phase.

Another study appears to indicate indirectly that OCs might increase EE. Wallace et al (10) reported that OC users (n = 403) had a decreased body mass index (BMI) and triceps skinfold thickness compared with non-OC users (n = 998), whereas energy intake per kilogram of body weight was significantly greater in the OC users. Although these findings suggest a greater EE in the OC users, measurement of these indexes was not included. In summary, it appears that OC use may affect components of the energy-balance equation. However, there are problems with such studies because of small sample sizes, inconsistent testing protocols, and conflicting results.

Studies of the effects of OCs are hampered by the ≥22 different formulations of OCs currently in use (13). In the past, studies did not attempt to restrict investigations to OCs with the same formulation, making comparisons across investigations difficult, if not impossible (2). In addition, many of the OCs studied in the past are no longer on the market. The present study was designed to study the effect of the use of one OC formulation on the major components of the energy-balance equation.

SUBJECTS AND METHODS

Subjects

Selection criteria were strict to ensure that the women in the OC and non-OC groups were similar for several variables. Age was restricted to 18–35 y to exclude women that might be entering the early phases of menopause and to decrease the effect of age on metabolic rate (14). To decrease the variability in body weight, BMI (in kg/m²) was restricted to values between 19 and 25. Women were required to be nulliparous and OC users must have used only triphasic OCs and done so continuously for ≥6 mo. Women that reported being diagnosed previously with an eating disorder or currently on a therapeutic or weight-reducing diet were also excluded. Because the measurement of circulating hormone concentrations was not possible, only non-OC users who reported menstrual cycle lengths between 26 and 30 d were recruited. Women with cycles in this range should have phases of approximately the same timing and duration (15). Only nonsmoking subjects were included and all subjects reported being in good general health and that they were not consuming any medications that would affect weight or metabolic rate.

Informed consent was obtained before subjects began the study. The requirements, benefits, and risks involved in the study were explained to potential subjects in a group setting. Subjects were then given time to read over a copy of the informed consent form, were encouraged to ask questions, and were given an extra copy for their files.

Thirty-nine women meeting the above criteria agreed to participate in the study. Thirty-two subjects completed all phases. Three women had cycle lengths that fell outside the study criteria; two subjects dropped out during month 1 because they lacked interest; one person was disqualified at the orientation for medical reasons; and one person was injured in a car accident and had to withdraw, resulting in a sample of 17 in the OC group and 15 in the non-OC group. The OC group reported that they had taken Ortho-Novum 7/7/7 (O-N 7/7/7; Ortho Pharmaceuticals, Raritan, NJ) an average of 2.5 y.

Laboratory visit schedule

Month 2 laboratory visits were scheduled to coincide with the major peaks and nadirs in hormone fluctuations throughout the menstrual cycle and one visit was scheduled during each phase. EE measurements for each phase were conducted using the following guidelines: menses—days 2, 3, or 4 of menstrual flow; follicular—days 7, 8, or 9 of cycle; ovulation—within 48 h of a positive ovulation test in the non-OC group and on days 13, 14, or 15 of cycle for the OC group; luteal—days 22, 23, or 24 of cycle. For each subject, phase days were defined in the following ways: menses—the days of reported bleeding; follicular—the day after bleeding stops until the day before ovulation (for non-OC users) or through day 13 (for OC users); ovulation—the day of a positive ovulation test plus the following day (for non-OC users) or days 14 and 15 (for OC users); and luteal—the days after ovulation and preceding the onset of bleeding for the next cycle.

Oral contraceptives

O-N 7/7/7 was chosen for this study because it was the most widely prescribed OC at the time of the study (16). O-N 7/7/7 is a 28-d regimen OC that contains a constant low dose of 35 μg ethinyl estradiol for 21 d of the cycle with a trilevel (stepwise) adjustment of progestin. Pills for the first 7 d contain 0.5 mg norethindrone as the progestin, pills for the next 7 d contain 0.75 mg norethindrone, and pills for the last 7 d of active pills contain 1.0 mg norethindrone. Pills for the final 7 d of the 28-d pill cycle are placebo. The onset of menses usually occurs within 2–3 d after cessation of the pills containing active ingredients. The average cycle length with use of O-N 7/7/7 is 28.0 ± 4.6 d (17).

Height, weight, and BMI

Height was measured by using a sliding stadiometer that was attached to a Detecto Electronic Scale (model no. 8430; Webb City, MO); weight was also measured with the scale. BMI was calculated from height and weight measurements by dividing weight by height squared.

Ovulation prediction kits

In non-OC users luteinizing hormone rises 24–48 h before ovulation, which generally occurs around days 13–15 of the menstrual cycle. This can be determined through the use of home ovulation test kits that use an enzyme-linked immuno-adsorbent assay to detect the presence of luteinizing hormone in the urine (18–20). Subjects began testing on day 9 of their menstrual cycle and continued until a positive test was obtained.

Daily food records

Training for completing daily food records occurred during an orientation session and was conducted by graduate-level nutrition students. The trainer discussed the need to provide careful estimations of portion size without actually weighing and measuring each food and beverage. Food models and
serving tools (eg, tablespoons, bowls, glasses) were used to demonstrate serving sizes, and subjects were provided with shortcuts for estimations, eg, 3 oz (85.05 g) of meat is the size of a deck of cards. Subjects practiced estimating portions. The trainer discussed the necessity of providing details regarding preparation and items that might be added to a food or beverage, and examples of good records were presented so that subjects could see the level of detail needed. Subjects recorded intake for 5 d during the practice month. These records were checked for completeness, and retraining was done if needed. Subjects recorded their intake each day during their next menstrual cycle. Records were brought to each laboratory visit, at which time they were checked for completeness. Records were coded by graduate-level nutrition students and analyzed by using the DINE 3.4 nutritional analysis program (21). Total energy intake and the percentage of energy from fat, carbohydrate (complex and added sugar), and protein was obtained for each day’s intake, and means were computed by phase for each subject. The number of records analyzed for each phase varied by the number of days each subject spent in each phase.

Measurement of energy expenditure

Indirect calorimetry was used to determine REE. The canopy method of the Critical Care Management (CCM) Desktop Analysis system metabolic cart was used (22). Because indirect calorimetry is valid only while the patient is in a steady state (22), the first 5 min of the 25-min testing period were excluded from analysis (23). Testing was performed with subjects in the supine position in rooms where the temperature and light were held constant. Before measurement of REE, oral temperatures of subjects were measured to ensure that they had no elevations of body temperature that would elevate EE (24).

Subjects were asked to keep a daily log of their activity during the assessment month. This log was derived from the Stanford Activity Recall developed by Blair et al (25) and gathers information on activity and sleep patterns. The original measure asks the subject to recall this information for the previous 7-d period, but the time between laboratory visits in the present study varied greatly so we devised a daily log format. At each laboratory visit the logs were reviewed with the subject and complete information was obtained for all days of the cycle.

Procedures

Subjects were followed for two complete menstrual cycles. Month 1 was a practice month during which subjects monitored their menstrual cycle and practiced using ovulation test kits (for the non-OC group) and recording dietary intake for 5 d; they also had one REE measurement. This REE test was conducted to acclimate the subject to the procedure; the information was not used in data analysis.

In month 2, subjects began recording dietary intake and physical activity on the first day of menses and continued daily recording for their entire cycle. Participants made four laboratory visits during month 2. At each laboratory visit, subjects were weighed, food records were checked for accuracy, physical activity records were reviewed, and REE was measured. Subjects had fasted since 2200 the evening before each visit. All visits took place between 0600 and 1000.

Statistical analysis

Independent t tests were conducted for baseline variables. Dietary intake, metabolic rate, and physical activity data were analyzed by using repeated-measures analysis of variance. Age and BMI were entered in the preliminary analyses as covariates and, when significant, were retained in the final analysis. The homogeneity of regression slopes was tested for a differential effect of significant covariates on the dependent variables, and the within-cells correlations between each dependent variable and the covariates were calculated. Software programs from SPSS Inc (Chicago) and SAS Institute Inc (Cary, NC) were used for the analyses.

RESULTS

Results indicated no significant differences between OC and non-OC users in age, weight, height, and BMI at baseline, nor in length of menstrual cycle during the testing month (Table 1). Differences between groups in energy intake and percentages of carbohydrate, fat, and protein were examined by phase. Means ± SDs for total energy intake are shown in Table 2. Age was a significant covariate, so values were adjusted for age. The test for homogeneity of regression slopes indicated a differential effect of age on the luteal phase between the two groups. The within-cell correlation between age and total energy was 0.37. Results of the repeated-measures analysis of variance for total energy intake indicated no significant effect for group or phase but a marginal interaction between group and phase: F11, 301 = 1.08 (P = 0.31), F13, 281 = 1.39 (P = 0.25), and F13, 281 = 2.56 (P = 0.06), respectively.

Analysis of the composition of nutrients was conducted by comparing the percentages of energy consumed from protein, fat, and carbohydrate across the menstrual cycle by phase. The comparisons of percentage of energy from protein are presented in Table 3. Both the group effect and interaction between group and phase were not significant: F11, 301 = 0.12 (P = 0.74) and F13, 281 = 0.58 (P = 0.63), respectively. However, analysis by phase for percentage of energy from protein consumed showed significant differences (F13, 281 = 4.18, P = 0.008). Tukey’s multiple-range follow-up test was run to determine the differences in protein consumed across phase. The entire sample consumed significantly less energy from protein during menses than in all other phases. BMI was a significant covariate, so values in Table 3 were adjusted for BMI. The test for homogeneity of regression slopes indicated no differential effect of BMI on any phase between the two

| Table 1 Physical characteristics of the group of users (OC) and nonusers (non-OC) of oral contraceptives\(^7\) |
|---------------------------------|-----------------|-----------------|
|                                | OC group \((n = 17)\) | Non-OC group \((n = 15)\) |
| Age (y)                        | 21.7 ± 3.2       | 19.9 ± 3.1       |
| Height (cm)                    | 164.0 ± 2.0      | 166.5 ± 2.7      |
| Weight (kg)                    | 59.8 ± 5.5 (42.1-70.6) | 57.3 ± 10.4 (50.5-69.8) |
| BMI (kg/m\(^2\))               | 22.2 ± 2.3 (17.3-26.0) | 20.8 ± 2.8 (18.1-25.1) |
| Length of cycle (d)            | 28.2 ± 1.6       | 27.3 ± 1.8       |

\(^7\)\(x\) ± SD; range in parentheses. There were no significant differences.
TABLE 2

Total energy intake in the group of users (OC) and nonusers (non-OC) of oral contraceptives

<table>
<thead>
<tr>
<th>Phase</th>
<th>OC group (n = 17)</th>
<th>Non-OC group (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Menses</td>
<td>7.9 ± 1.3 [69]</td>
<td>7.0 ± 1.3 [77]</td>
</tr>
<tr>
<td>Follicular</td>
<td>7.5 ± 1.2 [152]</td>
<td>6.7 ± 1.5 [127]</td>
</tr>
<tr>
<td>Ovulation</td>
<td>7.3 ± 1.2 [34]</td>
<td>7.8 ± 2.4 [30]</td>
</tr>
<tr>
<td>Luteal</td>
<td>8.0 ± 1.4 [223]</td>
<td>7.4 ± 1.5 [176]</td>
</tr>
</tbody>
</table>

\[ \bar{x} \pm SD; \text{number of days of diet records for each group in brackets.} \]

TABLE 3

Protein intake in the group of users (OC) and nonusers (non-OC) of oral contraceptives

<table>
<thead>
<tr>
<th>Phase</th>
<th>OC group (n = 17)</th>
<th>Non-OC group (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Menses</td>
<td>12.6 ± 2.4 [69]</td>
<td>12.7 ± 3.3 [77]</td>
</tr>
<tr>
<td>Follicular</td>
<td>13.8 ± 1.9 [152]</td>
<td>14.1 ± 2.6 [127]</td>
</tr>
<tr>
<td>Ovulation</td>
<td>14.3 ± 2.9 [34]</td>
<td>13.6 ± 3.1 [30]</td>
</tr>
<tr>
<td>Luteal</td>
<td>14.5 ± 2.3 [223]</td>
<td>13.8 ± 2.7 [176]</td>
</tr>
</tbody>
</table>

\[ \bar{x} \pm SD; \text{number of days of diet records for each group in brackets.} \]

TABLE 4

Fat intake in the group of users (OC) and nonusers (non-OC) of oral contraceptives

<table>
<thead>
<tr>
<th>Phase</th>
<th>OC group (n = 17)</th>
<th>Non-OC group (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Menses</td>
<td>32.5 ± 5.7 [69]</td>
<td>28.6 ± 8.4 [77]</td>
</tr>
<tr>
<td>Follicular</td>
<td>32.4 ± 3.9 [152]</td>
<td>28.8 ± 7.3 [127]</td>
</tr>
<tr>
<td>Ovulation</td>
<td>34.1 ± 7.0 [34]</td>
<td>28.6 ± 5.8 [30]</td>
</tr>
<tr>
<td>Luteal</td>
<td>35.2 ± 6.1 [223]</td>
<td>28.5 ± 6.9 [176]</td>
</tr>
</tbody>
</table>

\[ \bar{x} \pm SD; \text{number of days of diet records for each group in brackets.} \]

DISCUSSION

In the present study, interesting and potentially weight-affecting differences were found between the two groups. Although there were no differences in total energy intake, there was a marginally significant interaction between group and phase, indicating that the two groups had different patterns of energy intake across the cycle. Composition of intake also appeared to differ. Results indicated that OC users had a larger percentage of their intake from fat and a lower percentage of their intake from carbohydrate than did non-OC users. Both groups consumed less protein during meals than during the other phases of the cycle. No significant differences were found in REE (total MJ/d) between phases or across the cycle. Both groups reported marginally more activity (P = 0.09) during menses than during the luteal phase.

Our results indicate that OC users and non-OC users did not have significant differences in total energy intake but reported qualitative differences in their intake. This finding agrees with previous findings by McNeill et al (11) but are contrary to...
TABLE 6

Resting energy expenditure in the group of users (OC) and nonusers (non-OC) of oral contraceptives

<table>
<thead>
<tr>
<th>Phase</th>
<th>OC group (n = 17)</th>
<th>Non-OC group (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Menses</td>
<td>6.0 ± 0.7</td>
<td>5.9 ± 0.7</td>
</tr>
<tr>
<td>Follicular</td>
<td>6.0 ± 0.9</td>
<td>5.6 ± 0.5</td>
</tr>
<tr>
<td>Ovulation</td>
<td>5.8 ± 0.7</td>
<td>6.0 ± 0.5</td>
</tr>
<tr>
<td>Luteal</td>
<td>6.1 ± 0.7</td>
<td>6.2 ± 0.9</td>
</tr>
</tbody>
</table>

* ± SD. There were no significant differences and age was a significant covariate, *P* = 0.05.

TABLE 7

Physical activity in the group of users (OC) and nonusers (non-OC) of oral contraceptives

<table>
<thead>
<tr>
<th>Phase</th>
<th>OC group (n = 17)</th>
<th>Non-OC group (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Menses</td>
<td>34.7 ± 3.4</td>
<td>35.3 ± 2.2</td>
</tr>
<tr>
<td>Follicular</td>
<td>34.4 ± 1.7</td>
<td>34.5 ± 1.8</td>
</tr>
<tr>
<td>Ovulation</td>
<td>34.5 ± 4.3</td>
<td>35.4 ± 2.9</td>
</tr>
<tr>
<td>Luteal</td>
<td>33.6 ± 1.3</td>
<td>34.1 ± 1.6</td>
</tr>
</tbody>
</table>

* ± SD. There was a marginal effect for phase (*P* = 0.09), with women exercising more in the menses than in the luteal phase. METS, metabolic equivalents.

those by Wallace et al (10), who found total energy intake to be significantly greater in OC users. There are several methodologic differences between this study and previous studies. One important difference is sample size. Wallace et al (10) had an extremely large sample (*n* = 1060) whereas McNeeil et al (11) had a very small sample (*n* = 5). The present study, although it had a relatively small sample size (*n* = 32), sought to increase statistical power by incorporating several controls to decrease variability. However, variability within each group was still large, producing little statistical power to detect differences.

An issue warranting future study is the decreased variability in energy intake seen in the OC group. The SDs in the OC group (range: 1.2–1.4 MJ) are clearly smaller than those in the non-OC group (range: 1.3–2.4 MJ). This decreased variability seen in the OC group may be related to the steady delivery of exogenous hormones. Decreased variability will lead to an increase in power so that, if the question under study does not relate to OC use, women taking OCs might prove to be a better study group.

Comparisons of macronutrient selection across phases between the two groups showed that the OC group consumed more energy from fat and less from carbohydrate consistently across phases compared with the non-OC group. There were no group effects for protein. These differences in dietary composition were dramatic, with the consumption of energy from fat ranging from 32.4% to 35.4% in the OC group and from 28.5% to 28.8% in the non-OC group. Such differences place the OC group at risk both for weight gain and, potentially, future health risks. Differences in carbohydrate consumption would have the same effect. Although the OC group derived from 47.6% to 51.9% of their intake from carbohydrate, the non-OC group consistently obtained > 55% of their intake from carbohydrate.

Previous work in animal models suggested that gonadal hormones may have “qualitative” effects on food intake (26) similar to these findings. This conclusion conflicts with that in the study by Wallace et al (10), in which no significant differences in macronutrient intakes were noted. However, subjects in that study reported intakes for only 1 d, which meant that different phases of the menstrual cycle were represented, thereby introducing more variability and reducing the chance of finding a difference. The possibility that OC use influences dietary composition should be studied further.

Comparisons between the present study and earlier studies are complicated by the methods used to assess dietary intake. Information regarding energy intake in the previous studies were compiled either from one 24-h recall (10) or by 7-d weighed records of energy intake (11). Although Wallace et al (10) had a very large sample, a single 24-h recall may not be an adequate assessment of intake (27). Although every recording method has its limitations, the daily food records used in the present study are still considered to be the best method for assessing dietary intake (28).

Earlier published reports suggest that OC use diminishes the increase in REE expected during the luteal phase (12). Had the present investigation studied only the follicular and luteal phases, our conclusions might have been the same. Although no significant differences were shown, the results in Table 6 suggest that the pattern of REE for the two groups was different: REE increased in the non-OC group from 5.6 to 6.2 MJ/d from the follicular to the luteal phases and REE remained virtually constant (from 6.0 to 6.1 MJ/d across the two phases) in the OC group. However, the means for the entire cycle in Table 6 suggest that, rather than a failure of the OC group to increase their REE in the luteal phase, it may actually have been a failure of the OC group to show the expected decrease in REE in the follicular phase. Interestingly, this is exactly the same pattern that was found in an examination of REE differences across the menstrual cycle in smokers and nonsmokers (29). In that study, none of the subjects were using OCs and the nonsmoking group (which would be equivalent to the non-OC group in the present study) also showed a decrease in REE during the follicular phase whereas the smoking non-OC group (like the OC group in the present study) had a relatively constant REE across phases. Thus, it may be that exogenous factors (such as hormones or nicotine) may affect REE by thwarting a normal decrease during the follicular phase. In both cases, this would have the effect of moving the energy-balance equation in a direction that would favor weight loss.

The present investigation represents the first examination of differences in physical activity between OC users and a group of women that have never used OCs. Although the entire sample had less physical activity in the luteal than in the menses phase, there were no significant differences between the groups. This finding is not surprising given the numerous symptoms that women report in the luteal portion of the cycle (30). No between-group differences for phases were found.

In summary, it appears that the OC users in the present study differed significantly from non-OC users in that they consumed a larger percentage of energy from fat and a lesser percentage of energy from carbohydrate. Given the similarity to earlier findings, the pattern of REE across the cycle in the two groups bears further investigation, even though the differences were not significant in our sample. Curiously, if future investigations do find that there is a diminished “dip” in REE during the follicular phase in OC users, these findings would have con-
tradiory effects on body weight. There is evidence that, independent of total energy intake, fat intake predicts increased body weight (31, 32). However, a metabolic rate that fails to decline during the follicular phase would seem to favor weight loss; although this effect might be expected to be subtle. Implications for energy-balance studies are not clear. It is possible that these shifts in energy balance work together to maintain body weight in the OC group because the two groups in the present study did not differ significantly in body weight (Table 1). However, it is also possible that a longitudinal investigation would find that this shift in energy balance favored a larger weight gain across time in the OC group. Our finding that there were significant differences in dietary intake between the OC users and non-OC users would, at the very least, argue for balancing research groups on OC use.

This study differs from earlier investigations in two important ways. First, criteria for participation were strictly controlled so that subjects were similar for several variables. Second, the entire menstrual cycle was studied. Earlier investigations have studied only one or two phases. Both of these design improvements should have increased our ability to detect differences by increasing the stability of our measures and decreasing the variability within our groups. However, the present study had several limitations. First, only one OC (O-N 7/7) was used and our results do not necessarily generalize to other OC formulations. Additionally, actual hormone concentrations were not assessed. Although the present study improved the assessment by limiting subjects to those with cycle lengths between 26 and 30 d, only an actual measurement of hormones ensures that women are at comparable points in their cycle. Careful monitoring of compliance with OC use would also have increased confidence that the OC group was actually ingesting the expected amount of hormones.

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