Effects of Oral Contraceptives on Free Fatty Acid Metabolism in Women

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These studies examined whether women using oral contraceptives have abnormalities in free fatty acid (FFA) metabolism compared with women not using oral contraceptives. Plasma palmitate kinetics ([^{3}H]palmitate) were measured at rest, following glucose ingestion, and during epinephrine infusion in 13 oral contraceptive users and 13 matched women not using oral contraceptives. Oral contraceptive users had significantly greater plasma triglyceride concentrations and glucose responses to oral glucose tolerance testing. No differences in basal (2.1 ± 0.1 *v* 1.8 ± 0.2 μmol · kg fat-free mass · FFM^{-1} · min^{-1}), glucose-suppressed (0.6 ± 0.1 *v* 0.5 ± 0.1 μmol · kg FFM^{-1} · min^{-1}), or epinephrine-stimulated (3.3 ± 0.1 *v* 3.6 ± 0.2 μmol · kg FFM^{-1} · min^{-1}) palmitate flux were detected between women using and not using oral contraceptives. The respiratory quotient (RQ) also was not different between groups. We conclude that the increase in plasma triglycerides and the mild glucose intolerance seen with oral contraceptive use is not associated with significant abnormalities of FFA metabolism.

WOMEN USING ORAL CONTRACEPTIVES have higher plasma triglyceride concentrations[1-3] than nonusers, as well as slightly greater plasma glucose and insulin responses to oral glucose tolerance testing.[2,4] These effects are common to many types of oral contraceptives[1,2,5,6] and could potentially be mediated by alterations in free fatty acid (FFA) metabolism. Some investigators have reported subtle differences in plasma FFA concentrations between oral contraceptive users and nonusers,[7-9] suggesting an influence of these medications on effective adipose tissue lipolysis. Although FFA turnover was not significantly different in women before and during oral contraceptive use in one small study,[10] our group[11-13] and others[14-17] have excluded women taking oral contraceptives from studies of FFA metabolism.

We began to question the presumption that oral contraceptives would modify FFA metabolism after finding that resting and stimulated FFA flux in women were the same in the follicular and luteal phases of the menstrual cycle.[18] The dramatic changes in plasma sex steroid concentrations between these two phases of the menstrual cycle are perhaps greater than could be expected with the use of oral contraceptives. A further challenge to this assumption was the statistically significant but relatively minor (10% to 20%) difference in FFA flux between estrogen-replaced and estrogen-deficient postmenopausal women.[19] Because relatively large differences in female sex steroid availability resulted in little[19] or no[18] detectable effects on FFA kinetics, we decided to reexamine the assumption that oral contraceptives influence FFA metabolism.

FFA release is a highly regulated process, which makes it important to assess the spectrum of conditions that alter FFA flux. We therefore examined FFA flux in women under overnight postabsorptive conditions, following glucose ingestion to suppress FFA release, and during an epinephrine infusion to stimulate lipolysis. Failure to detect an influence of oral contraceptives on adipose tissue lipolysis in all three conditions would be strong evidence against such an effect. We also tested whether differences in the respiratory quotient (RQ) are present between oral contraceptive users and nonusers. An elevated RQ would indicate reduced fatty acid oxidation, potentially creating the need for increased hepatic FFA reesterification and therefore increased hepatic triglyceride synthesis and secretion at the same relative FFA flux.

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SUBJECTS AND METHODS

Subjects

Informed written consent was obtained from 26 non-obese (body mass index, 18 to 25 kg/m^2) healthy premenopausal women. Half of the women were not currently using and had not used oral contraceptives for more than 1 year prior to the study, and half had been using oral contraceptives for more than 1 year before the study. All subjects had been weight-stable for 2 months before the study. The oral contraceptive preparations used by our volunteers contained 30 to 35 μg ethinyl estradiol and lower amounts (compared with older products) of progestins. The progesterone components were norethindrone (seven subjects), desogestril (three subjects), levonogestril (two subjects), and ethinodiol (one subject). A summary of the subjects' characteristics is provided in Table 1.

Materials and Assays

[9, 10-^{3}H]palmitate was obtained from Research Products International (St Louis, MO). Epinephrine (Abbott Laboratories, North Chicago, IL) and ascorbic acid (Cevalin; Eli Lilly, Indianapolis, IN) were used in these studies.

Plasma palmitate concentration and specific activity were determined by high-performance liquid chromatography (HPLC) using [$^2H_{31}$]palmitate as an internal standard.[20] Plasma insulin, C-peptide, and growth hormone concentrations were measured by radioimmunoassay as previously detailed,[11] plasma epinephrine and norepinephrine concentrations were measured using HPLC with electrochemical detection,[21] and plasma glucose concentrations were measured using a Beckman glucose analyzer (Palo Alto, CA). Body fat and fat-free mass (FFM) were measured by dual-energy x-ray absorptiometry (Lunar Radiation, Madison, WI) using software version 3.6. Plasma cholesterol, triglyceride, and high-density lipoprotein (HDL) concentrations were measured using previously described methods.[22] Oxygen consumption and CO_2 production rates were measured using a ventilated-hood technique (DeltaTrac Metabolic Cart; SensorMedics, Yorba Linda, CA).

Protocol

Each subject consumed a isocaloric diet containing 40% of calories as fat, 40% as carbohydrate, and 20% as protein in the General Clinical

Table 1. Characteristics of the Oral Contraceptive Users and Nonusers

Characteristic	OC Users	Nonusers
Age (yr)	28 ± 1	30 ± 2
Height (cm)	168 ± 1	166 ± 2
Weight (kg)	63.2 ± 1.7	58.8 ± 1.9
Body fat (%)	29 ± 2	28 ± 2
Cholesterol (mg/dL)	178 ± 13	154 ± 7
Triglycerides (mg/dL)	108 ± 12*	68 ± 8
HDL cholesterol (mg/dL)	53 ± 6	59 ± 5
FFM (kg)	44.7 ± 1.3	42.2 ± 1.2
Basal $\dot{V}O_2$ (mL/kg/min)	3.8 ± 0.1	3.6 ± 0.1

Abbreviations: OC, oral contraceptive; $\dot{V}O_2$, O_2 consumption.
*$P = .01$ *v* nonusers.

Research Center (GCRC) for 2 days prior to study. Because there is no effect of the menstrual cycle on FFA flux,[18] the studies were not scheduled with regard to the subjects' menstrual cycle. Oral contraceptive users were studied while taking the medication, but were not scheduled for a specific phase of the menstrual cycle. On the evening before the study, the subjects were admitted to the GCRC, where an intravenous catheter was placed in a forearm vein. The catheter was kept patent with a 30-mL/h infusion of 0.45% NaCl. The following morning after an overnight fast, a measurement of the resting energy expenditure was performed. A nonprimed, constant infusion of [9,10-^{3}H]palmitate (~0.3 μCi/min) was started 30 minutes prior to the first blood sample. A second intravenous catheter was placed retrogradely in a dorsal hand vein and placed in a warming box to obtain arterialized venous blood samples.[23]

A series of four blood samples were obtained at 10-minute intervals for measurement of the baseline plasma palmitate concentration and specific activity, plasma glucose, insulin, C-peptide, growth hormone, epinephrine, and norepinephrine concentrations. After these samples were obtained, the subjects consumed a glucose meal providing 1 g/kg glucose. Blood and breath samples were obtained at 30-minute intervals over the next 4 hours to assess the hormone and substrate response to the glucose load. Another set of blood samples were obtained at 10-minute intervals over the next 30 minutes to serve as a second baseline prior to the epinephrine infusion. For the last 90 minutes of the experiment, epinephrine was infused at 10 $ng \cdot kg^{-1} \cdot min^{-1}$. Blood samples were obtained at 15-minute intervals throughout the epinephrine infusion to assess the hormone and substrate response. A 30-minute breath sample was collected during the pre–epinephrine infusion baseline and the final 30 minutes of epinephrine infusion for measurement of O_2 consumption and CO_2 production.

Calculations

All values are presented as the mean ± SEM unless otherwise stated. The systemic palmitate rate of appearance (R_a) was calculated from the [^{3}H]palmitate tracer using a non–steady-state formula.[24] The baseline palmitate R_a was taken as the average of the four basal samples, the nadir meal palmitate R_a as the average of the three samples taken at maximal suppression of palmitate flux following glucose ingestion, and epinephrine-stimulated palmitate flux as the average of the last three samples obtained during epinephrine infusion.

To assess the integrated glucose and insulin response to the oral glucose tolerance test (OGTT), the area under the plasma glucose and insulin curve (trapezoidal rule) was calculated from time 0 through 270 minutes. The same approach was taken to assess the integrated suppression of palmitate R_a over the same time interval. To assess the integrated lipolytic response to epinephrine over the last 90 minutes of the experiment, the area under the palmitate R_a curve above baseline was determined.

Power Calculations and Statistical Analysis

Increased basal FFA flux in upper-body obese women (50% > nonobese women) is associated with hypertriglyceridemia and insulin resistance.[11] If oral contraceptives increase basal FFA flux by even half of this amount, we wished to be able to detect such an effect. We used data regarding the interindividual variability in basal FFA flux[11] to determine that the inclusion of 13 women in each group would provide 90% power to detect a 30% increase in FFA flux in the oral contraceptive users. To assess the statistical power of comparing postprandial suppression of FFA flux, we reviewed data from a previous study examining this issue in lean healthy men and women; [13] FFA flux was more suppressed in women than in men.[13] We wished to be able to detect an effect of oral contraceptives on postprandial suppression of FFA flux of a magnitude similar to that observed between men and women with at least 90% power. Thirteen women in each group were also sufficient to detect this difference.

To test the hypothesis that basal palmitate flux per kilogram FFM was different between women taking and not taking oral contraceptives, these values were compared using a nonpaired two-tailed *t* test. To address the hypotheses that the nadir and integrated (area under the palmitate R_a curve) post–glucose ingestion palmitate availability and the epinephrine-stimulated FFA flux were different between women taking and not taking oral contraceptives, a nonpaired two-tailed *t* test was also used. Likewise, other comparisons between groups (basal O_2 consumption and the RQ), as well as comparisons for plasma glucose and hormone concentrations, were made using a nonpaired two-tailed *t* test.

RESULTS

Subject Characteristics

The oral contraceptive users and nonusers were well matched for age, height, weight, percent body fat, FFM, and resting oxygen consumption (Table 1). Plasma triglyceride concentrations were significantly greater in oral contraceptive users versus nonusers (Table 1). Plasma lipid concentrations were otherwise comparable between the two groups. One woman in the oral contraceptive group inadvertently received one tenth of the intended oral glucose load, and her data are therefore not included in the glucose-response portion of this report.

Plasma Glucose, Hormone, and Catecholamine Concentrations

Baseline plasma glucose concentrations were identical in the two groups. Following glucose ingestion, plasma glucose increased to the same level in both groups, but decreased slightly more slowly in women taking oral contraceptives. The same pattern was observed for plasma insulin and C-peptide concentrations. The area under the plasma glucose curve (time 0 to 270 minutes) was greater ($P = .04$) in oral contraceptive users versus nonusers (1,700 ± 46 *v* 1,569 ± 38 $mmol/L \cdot 270\ min^{-1}$). The area under the plasma insulin concentration curve was greater in oral contraceptive users versus nonusers (40,880 ± 4,825 *v* 30,719 ± 3,975 $pmol/L \cdot 270\ min^{-1}$), but the differences were not statistically significant ($P = .12$) (Fig 1).

Plasma growth hormone concentrations were slightly but not significantly higher in oral contraceptive users versus nonusers throughout the study (Fig 1). Plasma epinephrine and norepinephrine concentrations in both groups are shown in Fig 2. There were no between-group differences in baseline, OGTT,

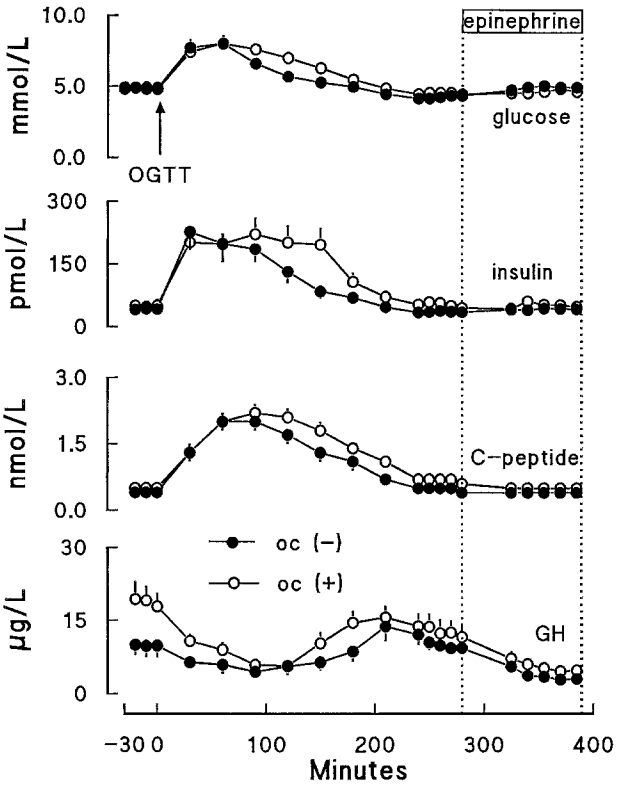

Fig 1. Plasma glucose, insulin, C-peptide, and growth hormone concentrations in oral contraceptive users (○) and nonusers (●) throughout the experiment. Oral glucose and the OGTT were administered at time 0. Epinephrine was infused for the last 90 minutes of the study.

recovery, or epinephrine-infused plasma catecholamine concentrations. As expected, plasma epinephrine concentrations were significantly higher during epinephrine infusion ($P < .001$) than during all other time intervals. When all women were considered together, plasma norepinephrine concentrations increased from the baseline to the OGTT time interval (0.63 ± 0.04 *v* 0.74 ± 0.04 nmol/L, respectively, $P < .001$) and were higher ($P < .01$) during epinephrine infusion (0.85 ± 0.06 nmol/L) than during the baseline interval.

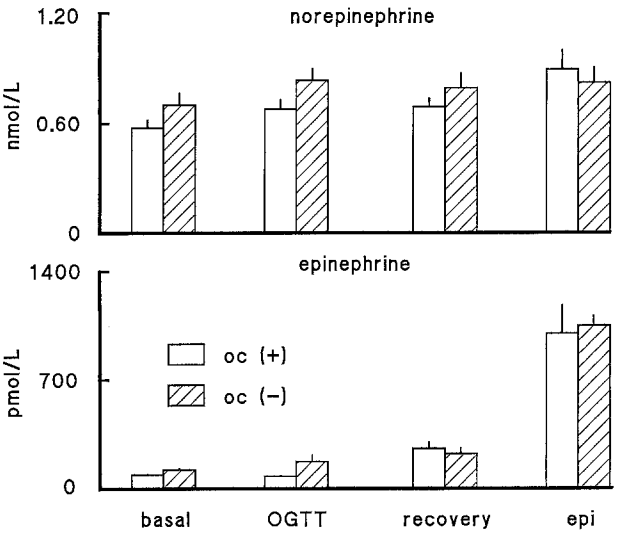

Fig 2. Mean plasma norepinephrine and epinephrine concentrations during basal, OGTT nadir, recovery, and epinephrine (epi) infusion time intervals. No significant between-group differences were present at any of the time intervals. OC, oral contraceptives.

Palmitate Kinetics

The plasma palmitate concentration and R_a throughout the study are depicted in Fig 3. The baseline plasma palmitate concentration in oral contraceptive users was 98 ± 8 (SD = 30) µmol/L, which was not different from that observed in nonusers, 85 ± 8 (SD = 29) µmol/L. Baseline palmitate flux was also comparable in oral contraceptive users and nonusers (2.1 ± 0.1 *v* 1.8 ± 0.2 µmol · kg FFM^{-1} · $Zmin^{-1}$, respectively, P = nonsignificant [NS]).

There were no significant differences in the nadir plasma palmitate concentration (20 ± 5 *v* 18 ± 4 µmol/L, respectively, P = NS) or flux (0.6 ± 0.1 *v* 0.5 ± 0.1 µmol · kg FFM^{-1} · min^{-1}, respectively, P = NS) following glucose ingestion. The area under the palmitate R_a curve for 270 minutes following glucose ingestion was not different between oral contraceptive users and nonusers (228 ± 22 *v* 255 ± 27 µmol · kg FFM^{-1} · 270 min^{-1}, respectively, P = NS).

Over the final 30 minutes of epinephrine infusion, the plasma palmitate concentration (204 ± 12 *v* 212 ± 11 µmol/L, respectively, P = NS) and palmitate flux (3.3 ± 0.2 *v* 3.6 ± 0.2 µmol · kg FFM^{-1} · min^{-1}, respectively, P = NS) were similar in women taking and not taking contraceptives. For the entire epinephrine infusion, the integrated palmitate R_a response (above baseline) was not different between groups (113 ± 17 *v* 104 ± 13 µmol · kg FFM^{-1} · 90 min^{-1}, respectively, P = NS).

Indirect Calorimetry Results

As noted, there were no significant differences in resting oxygen consumption between the two groups (Table 1). Likewise, the baseline RQ was not different between oral contraceptive users and nonusers. There were no significant differences in the RQ between oral contraceptive users and nonusers throughout the experiment (Fig 4).

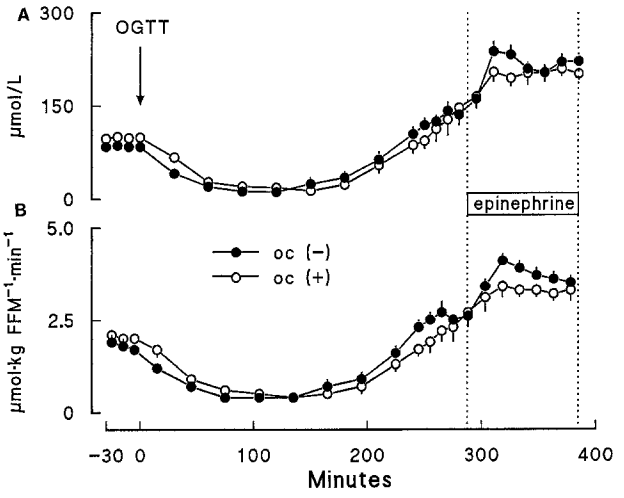

Fig 3. Plasma palmitate concentration (A) and R_a (B) in oral contraceptive users (○) and nonusers (●) throughout the experiment. At time 0, an OGTT was administered. Epinephrine was infused intravenously for the last 90 minutes of the experiment.

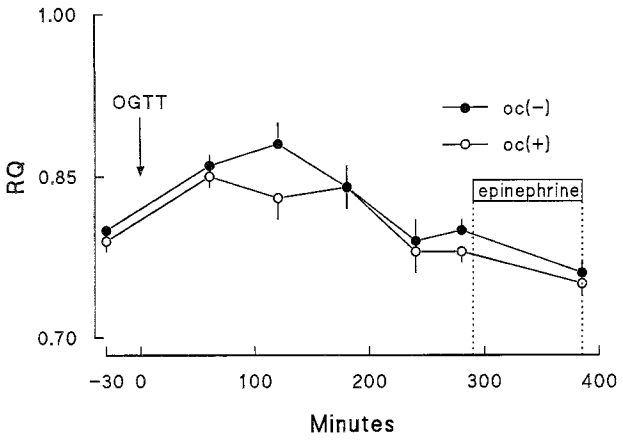

Fig 4. RQ values for oral contraceptive users (○) and nonusers (●) throughout the experiment. Administration of the OGTT and epinephrine are the same as in Fig 3.

DISCUSSION

These studies are the first to assess FFA kinetics in oral contraceptive users and nonusers under a variety of conditions. Palmitate flux was measured in women matched for age, weight, and body composition under basal, glucose-ingestion, and epinephrine-stimulated conditions. We found no significant differences in FFA flux between oral contraceptive users and nonusers under any of these conditions. Resting oxygen consumption and the RQ responses were not different between the two groups. These results strongly suggest that the hypertriglyceridemia and slightly greater plasma glucose response to glucose tolerance testing seen in women using oral contraceptives are not associated with significant abnormalities of effective adipose tissue lipolysis. Oral contraceptive use need not be an exclusion criterion for women participating in studies of FFA kinetics.

Our finding that basal FFA flux is not different in oral contraceptive users and nonusers confirms the findings of Hagenfeldt et al,[10] who reported that oleate flux was not different before and after 3 months of oral contraceptive use in five women. However, oleate flux was approximately 20% greater following oral contraceptive use, raising the possibility of a type 2 statistical error. The number of volunteers recruited to participate in the present study was selected to ensure sufficient statistical power to detect important differences in basal FFA flux, and to evaluate FFA kinetics under postprandial and catecholamine-stimulated conditions. Morrow et al[8] also found no statistically significant differences in basal or fasting plasma FFA concentrations between oral contraceptive users and nonusers, although plasma FFA concentrations are not always an ideal indicator of FFA kinetics.[19] More recently, Corssmit et al[9] noted significantly higher plasma FFAs in women than in men, as well as a lower RQ in women taking oral contraceptives. This is contrary to our past experience and the findings of this study. After 2 weeks of careful dietary control to ensure weight stability, men and women were found to have identical plasma FFA kinetics.[13] The RQ reported by Corssmit et al[9] for 16-hour fasted oral contraceptive users (~0.72) is substantially less than what we observed in our subjects after a 14-hour fast (~0.80). In the present study, subjects consumed a controlled diet prior to the experiment, whereas it is not clear whether the same precautions were taken by Corssmit et al.[9] Thus, it is possible that differences in the plasma FFA concentration and RQ between these two studies could be related to differences in prestudy dietary intake.

Palmitate was used as the FFA tracer in the present studies, as it has been shown to be a representative fatty acid for determining FFA flux.[25] However, differences in the oxidation of different fatty acids have been reported.[26] It is conceivable that palmitate oxidation may be different from that of other FFAs, and that its oxidation, or the oxidation of other fatty acids, could be altered by oral contraceptives. This seems unlikely, given that the systemic RQ was not different in oral contraceptive users and nonusers.

Basal palmitate flux was 15% greater in oral contraceptive users than in nonusers, and although not statistically significant, one might question whether this difference is sufficient to cause the hypertriglyceridemia or the mild increase in plasma glucose following glucose ingestion. This seems unlikely. A 15% between-group difference is small in comparison to the known intrasubject variation mean in FFA flux of 31% ± 21% (mean ± SD).[27] In addition, FFA flux and very-low-density lipoprotein (VLDL) production rates,[28] and therefore plasma triglyceride concentrations[29] are highly correlated. Plasma triglyceride concentrations in oral contraceptive users in the present study were about 40% greater than in nonusers. If the relationship between the FFA flux and VLDL triglyceride concentration in oral contraceptive users were similar to that reported by Kissebah et al[29] for patients with primary hypertriglyceridemia, the FFA flux should have been at least 40% greater than the control values in contraceptive users. This was clearly not the case, and suggests that if oral contraceptives stimulate hepatic VLDL triglyceride production, the effect is via a direct hepatic mechanism independent of systemic FFA availability.

Recent data suggest that even complete failure to suppress FFA concentrations does not significantly impair glucose tolerance if plasma insulin is allowed to increase normally following glucose ingestion.[30] This makes it very unlikely that the slightly greater basal FFA flux observed in oral contraceptive users caused the slight glucose intolerance we observed in this group. Note that the integrated suppression of palmitate flux following glucose ingestion was actually greater in oral contraceptive users than in nonusers, further discounting the possibility that impaired suppression of lipolysis could be responsible for the observed between-group differences.

Some of the differences between oral contraceptive users and nonusers in the present study are similar to those previously reported. For example, oral contraceptive users are often noted to have slightly higher plasma glucose and insulin concentrations during glucose tolerance testing.[2,4] Women taking oral contraceptives in the present study had higher plasma growth hormone concentrations, consistent with previous reports.[7,31] Plasma triglycerides are increased by a wide variety of oral contraceptive compounds,[1,3,4] and this was noted in the present study. We therefore believe that oral contraceptive users in this study displayed effects representative of the general metabolic response to these agents.

This study was not designed to determine whether institution of a specific oral contraceptive regimen would result in changes in FFA metabolism in women. Rather, we wished to test the hypothesis that oral contraceptive users would have substan-

tially different FFA kinetics than nonusers. We therefore selected women using a variety of low-dose estrogen oral contraceptives and a control group of women matched for age, height, weight, and body fat. A paired study design that assesses FFA kinetics in women starting or discontinuing oral contraceptives would not be appropriate to address our question. The progestin component of various oral contraceptives may differ with regard to androgenicity, which might have effects on FFA metabolism. To address this issue, a paired study of oral contraceptives containing progestins with greater and lesser androgenic properties would be necessary.

In summary, women taking oral contraceptives have similar rates of basal, post–glucose ingestion, and epinephrine-stimulated FFA flux. In addition, the RQ under these three conditions is comparable in the two groups of women, suggesting no effect of oral contraceptives on fatty acid oxidation. These findings were present in women who displayed the typical oral contraceptive effects on glucose tolerance and serum lipid concentrations. We conclude that oral contraceptive use has little or no effect on adipose tissue lipolysis. The changes in glucose tolerance and plasma triglyceride concentrations seen in oral contraceptive users are not likely due to effects on adipose tissue metabolism. Oral contraceptive users do not need to be excluded from studies of FFA metabolism. These results do not necessarily apply to postmenopausal women on estrogen replacement therapy, as no direct comparisons of FFA metabolism with premenopausal women have been performed.[19]

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