Effects of oral contraceptives on peak exercise capacity

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Casazza, Gretchen A., Sang-Hoon Suh, Benjamin F. Miller, Franco M. Navazio, and George A. Brooks. Effects of oral contraceptives on peak exercise capacity. J Appl Physiol 93: 1698–1702, 2002; 10.1152/japplphysiol.00622.2002.—We examined the effects of menstrual cycle phase and oral contraceptive (OC) use on peak oxygen consumption (V̇O₂ peak). Six moderately active, eumenorrheic women (25.5 ± 1.5 yr) were studied before and after 4 mo of OC. Subjects were tested during the follicular and luteal phases before OC and the inactive and high-dose phases after OC. Before OC, there were no significant differences between the follicular and luteal phases in any of the variables studied. There were also no differences between the inactive and high-dose phases. Dietary composition, exercise patterns, and peak heart rate, minute ventilation, and respiratory exchange ratio did not change with OC use. However, OC use significantly (P ≤ 0.05) increased body weight (59.6 ± 2.3 to 61.2 ± 2.6 kg) and fat mass (13.3 ± 1.3 to 14.5 ± 1.3 kg) and decreased V̇O₂ peak (−11%, 2.53 ± 0.21 to 2.25 ± 0.18 l/min). In conclusion, 1) endogenous ovarian steroids have little effect on V̇O₂ peak but 2) the exogenous ovarian steroids in OC decrease peak exercise capacity in moderately physically active young women.

peak exercise capacity in women could vary owing to ovarian hormone influences on stroke volume, pulmonary minute ventilation, oxygen-carrying capacity, blood flow, and muscle oxygen utilization. Although the cyclic endogenous ovarian hormone fluctuations across the normal menstrual cycle do not appear to affect V̇O₂ peak (1, 6, 12), low-dose administration of exogenous estrogen and progesterone may have a greater influence on exercise capacity. Only a few studies have examined the effects of exogenous steroids on exercise performance by use of longitudinal study designs. Although short-term OC use (21 days) did not affect V̇O₂ peak (2), 6 mo of monophasic OC use was associated with a significant decrease in V̇O₂ peak in endurance-trained women (18).

To our knowledge, no longitudinal studies have examined peak exercise capacity in moderately trained women before and after triphasic OC use. With monophasic OCs, the amounts of estrogen and/or progesterin vary across the pill cycle and more closely mimic the ovarian hormone variation that occurs during the normal menstrual cycle. Triphasic OCs contain lower per-cycle progestin levels to provide better cycle control and reduce the incidence of androgenic side effects such as alterations in carbohydrate and lipid metabolism (4) and therefore may not have the same influence on exercise capacity as monophasic OCs. The purpose of this investigation was to examine the effects of menstrual cycle phase (endogenous ovarian hormones) and triphasic OC use (exogenous ovarian hormone analogs) on peak exercise capacity, as measured by V̇O₂ peak.

MATERIALS AND METHODS

Subjects. Eight subjects were recruited from the University of California, Berkeley campus, to participate in a series of experiments to examine the effects of ovarian hormones on cardiorespiratory function and substrate utilization during peak and prolonged submaximal exercise. Results from the submaximal exercise trials on normally menstruating women before and after triphasic OC use. With monophasic OCs, the amounts of estrogen and/or progesterin vary across the pill cycle and more closely mimic the ovarian hormone variation that occurs during the normal menstrual cycle. Triphasic OCs contain lower per-cycle progestin levels to provide better cycle control and reduce the incidence of androgenic side effects such as alterations in carbohydrate and lipid metabolism (4) and therefore may not have the same influence on exercise capacity as monophasic OCs. The purpose of this investigation was to examine the effects of menstrual cycle phase (endogenous ovarian hormones) and triphasic OC use (exogenous ovarian hormone analogs) on peak exercise capacity, as measured by V̇O₂ peak.

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women (22) are reported separately. Retrospective blood analyses revealed that two of the subjects failed to meet the ovarian hormone concentration criteria for the follicular and luteal phases of the menstrual cycle and thus were excluded from data analysis. The final subject pool, for peak exercise analysis, consisted of six healthy, nonsmoking, female subjects (25.5 ± 1.5 yr). Subjects habitually exercised 2–6 h/wk (3.5 ± 0.6 h/wk) but were not competitive athletes. The women were nulliparous; had been diet, weight, and exercise stable; and had not taken OCs for at least 6 mo. All subjects reported consistently normal menstrual cycles (22–32 days) and were injury and disease free as determined by health history questionnaire and physical examination. Informed, written consent was provided, and the University of California Committee for the Protection of Human Subjects approved the study protocol (no. 2001-8-132).

**Experimental design.** Physical work capacity and VO2 peak were tested, in a randomized order, during the early follicular (FP, 4–8 days after the start of menses) and midluteal (LP, 17–25 after the start of menses and 6–9 days after ovulation) phases of the menstrual cycle before OC use. Ovulation was determined by using urine ovulation predictor kits (First Response, Carter Products, New York, NY). FP and LP were confirmed by plasma estradiol and progesterone concentrations from blood samples taken at rest before the peak exercise test or from blood sampled at rest on the same day of the next menstrual cycle. Progesterone levels above 3 ng/ml were used for verification of the luteal phase (21). Peak exercise testing was completed within one to two sequential menstrual cycles.

After completion of the menstrual cycle phase testing, each subject began taking the same triphasic OC (one pill per day) for four complete cycles (28 days per cycle). For days 1–7 each pill contained 0.035 mg ethinyl estradiol and 0.18 mg norgestimate, for days 8–14 each pill contained 0.035 mg ethinyl estradiol and 0.215 mg norgestimate, for days 15–21 each pill contained 0.035 mg ethinyl estradiol and 0.25 mg norgestimate, and for days 22–28 the pills were absent of synthetic hormones. Physical work capacity and VO2 peak were reassessed during the week of the inactive pills (IP) and during the second week of active pill ingestion (HP).

Subjects were instructed to refrain from exercise, caffeine, and medications 24 h before testing, to eat a light meal 3 h before arriving at the laboratory, and to maintain constant diet and exercise regimens throughout the entire experimental period. Three-day dietary records were collected and analyzed before and after the 4 mo of OC using the Nutritionist III program (N-Squared Computing, Salem, OR).

**Peak exercise tests.** Before each peak exercise test, subjects were weighed and body composition was determined (six-site skinfolds with a Harpenden skinfold caliper) (9). A continuously graded exercise test was conducted on an electronically braked cycle ergometer (Monark Ergometric 839E, Vansbro, Sweden). The workload began at 75 W and was increased by 25 W every 3 min until volitional exhaustion. The test was considered maximal if respiratory exchange ratio values exceeded 1.1. Respiratory gases were continuously collected and analyzed via an open-circuit indirect calorimetry system (Ametek S-3A1 O2 and Ametek CD-3A CO2 analyzers, Pittsburgh, PA), and respiratory parameters were recorded every minute by a real-time, on-line personal computer-based system. Heart rate was continuously monitored by a Quinton Q750 electrocardiograph (Bothell, WA).

**Blood sampling and analyses.** Blood was sampled at rest and immediately transferred to collection tubes containing EDTA for hormone determination. Plasma estradiol and progesterone concentrations were determined by 125I radioimmunoassay (Coat-A-Count kits; Diagnostic Products, Los Angeles, CA). All samples for each subject were analyzed together. The intra-assay coefficients of variation were 1–5%.

**Statistical analyses.** Repeated-measures ANOVA and Fisher’s protected least significant difference post hoc tests were used to determine phase differences in body weight, body composition, diet composition, estradiol and progesterone concentrations and peak power output, heart rate, pulmonary minute ventilation, oxygen consumption rate, carbon...
dioxide production, and respiratory exchange ratio by use of Statview 5.0.1 (SAS Institute, Cary, NC). Results are expressed as means ± SE throughout the text. The significance level was set at α < 0.05.

RESULTS

Subject characteristics. Subject characteristics for the six women that met the ovarian hormone criteria on the day of maximal exercise testing, for all phases, are presented in Table 1. Subject numbers and characteristics vary between the series of reports (22) from our laboratory because not all of the eight subjects met the phase criteria for every experimental protocol. There were no significant differences in body weight or body composition between FP and LP before OCs or between IP and HP with OCs, except a slightly higher fat mass in LP vs. FP. However, there was a small, but significant (P < 0.05), increase in body weight (3%) and fat mass (9%) after 4 mo of OC use.

There were no significant changes in total energy intake (1,920 ± 191 kcal before OC and 1,819 ± 260 kcal after OC), percentage of the energy intake as carbohydrate (58 ± 2.2% before OC and 54 ± 2.9% after OC), percentage of the energy intake as fat (27 ± 2.9% before OC and 31 ± 3.1% after OC), and percentage of the energy intake as protein (15 ± 1.6% before OC and 14 ± 1.3% after OC) with OC use.

Day of cycle, days past ovulation, and the ovarian hormone profiles for each phase are shown in Table 2. Criteria for FP (progesterone < 1 ng/ml) and LP (progesterone > 3 ng/ml) were met in six subjects before OC use. LP was associated with significantly higher (P < 0.05) estradiol and progesterone concentrations than all other phases. Both ovarian hormones were low after OC use, validating the suppression of endogenous hormone production by synthetic ovarian steroids.

Cardiorespiratory responses. At peak effort, there were no significant differences in any of the cardiorespiratory variables between FP and LP before OC use or between IP and HP with OC (Table 3). However, after 4 mo of OC use, there were significant decreases (P < 0.05) in time to peak exercise (14%) and in the peak power output attained (8%). There were also significant (P < 0.05) reductions in \( \dot{V}_{O_2} \) measured in both liters per minute (11%) and milliliters per kilogram per minute (13%) and in peak carbon dioxide production (15%). There were no significant changes in peak heart rate, pulmonary minute ventilation, and respiratory exchange ratio. All six subjects experienced a decline in \( \dot{V}_{O_2 \text{peak}} \) (ml·kg\(^{-1}\)·min\(^{-1}\)) after 4 mo of OC use (Fig. 1).

DISCUSSION

This study confirms that, in the absence of OCs, menstrual cycle phase does not affect peak exercise capacity, with no significant changes in body weight, body composition, or cardiorespiratory factors, including \( \dot{V}_{O_2 \text{peak}} \), between the follicular and luteal phases. However, 4 mo of a low-dose triphasic OC resulted in a significant increase in body weight and fat mass and a significant 11% decrease in \( \dot{V}_{O_2 \text{peak}} \) not normalized to body mass. There was no change in \( \dot{V}_{O_2 \text{peak}} \) between the inactive and high-dose phase with OCs, suggesting a persistent synthetic ovarian hormone effect despite a 1-wk cessation of ovarian steroid intake between cycles.

That OCs, but not luteal phase menstrual cycle variations in ovarian hormones, affected \( \dot{V}_{O_2 \text{peak}} \) suggests that steroid levels may be involved in suppression of peak exercise capacity. OCs mimic the estrogen profile in both liters per minute (11%) and milliliters per kilogram per minute (13%) and in peak carbon dioxide production (15%).
during pregnancy, with high levels of ethinyl estradiol (>300 pg/ml), levels that are much higher than observed during the normal menstrual cycle (24). As well, the type of contraceptive pill may have an effect on \( \dot{V}O_2 \text{peak} \). Our finding of an 11–13% decrease in \( \dot{V}O_2 \text{peak} \) in moderately trained women after 4 mo of triphasic OCs is greater than the 7% decrease in \( \dot{V}O_2 \text{peak} \) found in endurance-trained women with 6 mo of monophasic OCs (18). Moreover, C. M. Lebrun (unpublished observations) has observed a similar, small, but statistically significant decrease in \( \dot{V}O_2 \text{peak} \) with triphasic OC use in athletic women. And, finally, the duration of OC use may play a role. Longer than 1 mo of OC use appears to be necessary to induce physiological changes because a study examining 1–3 wk of monophasic OCs found no significant effect on \( \dot{V}O_2 \text{peak} \) (2).

Although the number of subjects was small in our investigation, every subject experienced a drop in \( \dot{V}O_2 \text{peak} \) with OC use, indicating a significant physiological effect. That \( \dot{V}O_2 \text{peak} \) was depressed during both IP (ethinyl estradiol levels \( \approx 8 \) pg/ml) and HP (ethinyl estradiol levels > 300 pg/ml) phases of OC use is taken to indicate persistence of OC effects (24). In agreement with our findings are those of Lynch et al. (14), who looked at the effects of long-term OC use on intermittent exercise performance in untrained women.

Factors that could reduce \( \dot{V}O_2 \text{peak} \) include decreases in stroke volume, oxygen-carrying capacity (hemoglobin levels), muscle blood flow, or oxygen extraction or changes in the pattern of substrate utilization. However, most of these do not appear to be candidates for an OC-induced negative effect on \( \dot{V}O_2 \text{peak} \). A decrease in stroke volume is unlikely because estrogen replacement therapy has been shown to increase stroke volume (10) and OC use has been shown to increase the activity of the renin-angiotensin-aldosterone system at rest (19). Decreased hemoglobin concentration is also unlikely because most studies have found no difference in resting blood hemoglobin and ferritin concentrations (11, 17) and an increase in serum iron levels (17) with OC use, presumably owing to a decrease in menstrual blood loss (11).

Although we did not directly assess sympathetic nervous system activity (SNA) in this study, decreased SNA and plasma catecholamine concentrations could explain the lower peak oxygen consumption observed with high ovarian hormone concentrations. Consistently high estrogen and progesterone concentrations, such as occur during pregnancy and with exogenous ovarian hormones, may blunt SNA and catecholamine levels as a protective mechanism to maintain blood flow to the uterus and prevent maternal hypoglycemia and uterine contractions (15).

Both the sympathetic nervous and endocrine systems play roles in maintaining normal blood glucose concentrations. Because catecholamines do not begin to rise in the circulation until the level of effort becomes strenuous (e.g., >65% \( \dot{V}O_2 \text{peak} \)), catecholamines are directly involved in glycogen mobilization during strenuous exercise. In contrast, hormones such as human chorionic somatotropin, growth hormone, cortisol, and thyroid hormone play roles in maintaining glucose homeostasis during pregnancy (15), and their importance is more likely exhibited during submaximal prolonged exercise. However, catecholamines are directly involved in hepatic and muscle glycogen mobilization during strenuous exercise. The fetus relies almost exclusively on maternal glucose for growth and development (15), and suppression of epinephrine and norepinephrine release could be a means of preventing maternal liver glycogen depletion and low blood glucose concentrations.

Pregnancy is associated with suppressed catecholamine levels during strenuous exercise (15), and exogenous estradiol administration has been shown to decrease SNA at rest (26), decrease catecholamine levels and glucose production and utilization during exercise (20), and increase the levels of the potent vasodilator nitric oxide (5). During exercise, increased SNA and the resultant vasoconstriction in nonactive tissue is essential for increasing blood flow to the working muscle. As exercise intensity increases, some vasoconstriction in the active muscle is also required to maintain mean arterial pressure. Blunting of SNA with high ovarian hormone concentrations, therefore, could limit peak exercise performance.

Although oral contraceptives decrease peak exercise capacity in moderately trained young women, effects of these synthetic steroid hormones on prolonged endurance exercise performance in competitive athletes are less obvious and warrant further investigation. The decrement in \( \dot{V}O_2 \text{peak} \) induced by OC use may subside over time or become insignificant owing to training-induced adaptations in highly trained female athletes.

In conclusion, these results suggest that 1) endogenous hormones have little effect on exercise performance as measured by \( \dot{V}O_2 \text{peak} \), but 2) low-dose triphasic OCs (exogenous ovarian hormones) appear to decrease peak exercise performance in moderately physically active young women.

NOTE ADDED IN PROOF

The number of subjects we studied was small, but similar results on the effects of OCs on \( V_{O2\text{max}} \) are reproducible. Since acceptance of our paper, we have learned that the work of Lebrun et al., cited as unpublished, is now in press (Lebrun CM, Petit MA, McKenzie DC, Taunton J, and Prior JC. Decreased \( V_{O2\text{max}} \) with triphasic oral contraceptive use in highly active women: a randomised controlled trial. Br J Sports Med In Press).

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