Decreased maximal aerobic capacity with use of a triphasic oral contraceptive in highly active women: a randomised controlled trial

C M Lebrun, M A Petit, D C McKenzie, J E Taunton, J C Prior

Background: Oral contraceptives are commonly used by women athletes. However, their effect on athletic performance is unclear.

Objectives: To examine the effects of a moderate dose, triphasic oral contraceptive on measures of athletic performance in highly trained women athletes.

Methods: This is a double blind, placebo controlled trial in 14 women with ovulatory menstrual cycles and maximal aerobic capacity ($V_{O2\text{MAX}}$) $\geq$ 50 ml/kg/min. Four measures of athletic performance were tested: $V_{O2\text{MAX}}$, anaerobic capacity (anaerobic speed test), aerobic endurance (time to fatigue at 90% of $V_{O2\text{MAX}}$), and isokinetic strength (Cybex II dynamometer). Height, weight, and six skinfold measurements were also recorded. All these observational tests were completed during both the follicular and mid-luteal phases of an ovulatory menstrual cycle. Cycle phases were confirmed by assaying plasma oestradiol and progesterone. Participants were subsequently randomly assigned to either a tricyclic oral contraceptive or placebo and retested in identical fashion (oral contraceptive phase).

Results: Absolute and relative changes in $V_{O2\text{MAX}}$ from follicular to oral contraceptive phase decreased in the oral contraceptive group by 4.7%, whereas the placebo group showed a slight increase (+1.5%) over the same time period. Two of the women taking oral contraceptive had decreases of 4 and 9 ml/kg/min. In contrast, most women in the placebo group improved or maintained $V_{O2\text{MAX}}$. There was also a significant increase in the sum of skinfolds in women taking oral contraceptive compared with those taking placebo ($p<0.01$). There were no significant changes in other physiological variables (maximum ventilation, heart rate, respiratory exchange ratio, packed cell volume) or measures of performance (anaerobic speed test, aerobic endurance, isokinetic strength) as a function of oral contraceptive treatment.

Conclusions: The decrease in $V_{O2\text{MAX}}$ that occurs when oral contraceptive is taken may influence elite sporting performance in some women. Further studies are required to determine the mechanisms of this change.

We previously reported observational changes in aerobic performance across the menstrual cycle in 16 highly trained female athletes. As an extension of that study, the same women were subsequently randomised to oral contraceptive or placebo for two months, and retested between days 14 and 17 of the second cycle. The purpose of this randomised double blind, placebo controlled study was to examine characteristics of athletic performance with oral contraceptive use in highly active women.

METHODS AND MATERIALS

Subjects
Ethical approval was obtained from the committee on human experimentation of the University of British Columbia, and all participants gave written informed consent. Athletic women aged 18–40 were recruited. Women were initially excluded if they did not meet the following criteria: (a) regular menstrual cycles (24–35 days in length); (b) no oral contraceptive use in the three months before entering the study; (c) participating on a regular basis in competitive aerobic activity—that is, running, cycling, triathlon, rowing, cross country skiing. At an initial screening session, $V_{O2\text{MAX}}$ and general health history were assessed. Volunteers who had $V_{O2\text{MAX}}$ values less than 50 ml/kg/min were excluded. Women were further excluded if they had any potential risk factors for oral contraceptive administration including smoking, any significant past medical condition, or were taking any medication that...
might interfere with exercise testing or administration of oral contraceptive. Participants were also required to have a physical examination, including a pelvic examination and Pap smear, carried out by their own doctor. Women taking supplements or iron were asked to maintain the exact dosage throughout the entire length of the three cycle study (of which this controlled trial was the third cycle).

Of the 51 volunteers for the initial study, 17 met all criteria and completed all three tests (follicular, luteal, and oral contraceptive or placebo). Three of these 17 women did not show hormonal evidence of ovulation during the observational study, and their test results were subsequently excluded from the analyses. Data are presented for 14 women who completed this controlled trial.

**Study design**

Figure 1 presents an overview of the study design and testing protocol. Testing was performed during both the early follicular (days 3–8) and mid-luteal (days 4–9 after “ovulation”) phases of an ovulatory menstrual cycle. A resting level of serum progesterone higher than 16 nmol/l was required to confirm ovulation. After follicular and luteal phase tests, participants were randomly assigned to either an oral contraceptive (n = 7) or placebo (n = 7) group. Participants and investigators were blind to group assignment.

A triphasic oral contraceptive (Synphasic; Pharmacia Canada, Mississauga, Ontario, Canada) was used. Synphasic contains a constant concentration of 0.035 mg ethinyl oestradiol and two different doses of norethindrone in three phases (days 1–7, 0.5 mg; days 8–16, 1.0 mg; and days 17–21, 0.5 mg) equalling a total norethindrone dose of 15.0 mg over the 21 day cycle. All women took an unmarked lactose capsule containing either oral contraceptive or placebo following the recommended schedule of daily administration for three consecutive weeks and stopping for one week. Capsules were taken as above for two consecutive months. The treatment testing session was performed between days 14 and 17 (mean (SD) 14.4 (0.5) days) of the second cycle of oral contraceptive or placebo administration (fig 1). These days were chosen as these were the last days of the highest progesterin dose of the triphasic oral contraceptive.

**Testing protocol**

All tests were completed on two successive days during each phase (follicular, luteal, and treatment). Because of the double blind nature of the study, treatment phase tests were conducted on days 14–17 of the cycle rather than based on day of ovulation. Although this may theoretically be during the luteal phase in the subjects on placebo, there was a high degree of individual variability in the actual day of ovulation. Most women were actually in the mid- or late-follicular phase according to serum progesterone levels. Two women in each group appeared to have ovulated before oral contraceptive treatment tests.

For the first day, participants reported to the laboratory in a fasted, resting state, and venous blood samples, VO2MAX, and anaerobic performance were assessed. Measurements of isokinetic strength, aerobic endurance, and assessment of body composition were completed on the second day of testing.

**Anthropometry and body composition**

Height and weight (Detecto industrial scale) were measured to the nearest 0.1 cm and 0.1 kg respectively. Skinfold thickness was measured at six sites (biceps, triceps, subscapular, suprailliac, anterior thigh, and medial calf) with a Harpenden skinfold caliper (John Bull, UK British Indicators Ltd, St Albans, Herts, UK). Skinfold measurements are reported as the sum of all values. Percentage body fat was assessed by underwater densitometry and calculated using the Siri formula.

**Blood samples**

Blood samples (15 ml) were obtained by venepuncture. They were kept cool (in an ice/water bath), and processed when testing was completed. One tube was taken to the laboratory at the University Hospital for determination of an automated blood count (CoulterS + STKR). The remaining blood was spun in a refrigerated centrifuge (Damon/IEC Clini-Cool) for 10 minutes at 3000 rpm. Plasma was stored in Venoject plain silicone coated glass tubes at −20°C until analysis using commercially available no extraction, solid phase radioimmunoassays (Coat-A-Count Estradiol and Coat-A-Count Progesterone; Diagnostic Products Corporation, Los Angeles, California, USA). Assay sensitivities were 2.9 pmol/l for oestradiol and 0.16 nmol/l for progesterone. The oestradiol assay does not detect the ethinyl oestradiol and the progesterone assay does not detect the norethindrone in this oral contraceptive.

**Aerobic capacity**

$V_{O_{2\text{MAX}}}$ was assessed using a standard running protocol. After a 10 minute warm up at a self selected pace (between 2.2 and 2.7 m/s), a continuous progressive workload was carried out on a level grade, beginning at a speed of 2.2 m/s, and increasing by 0.22 m/s each minute until fatigue. Heart rate was monitored using a Polar Vantage heart rate monitor and recorded at 45 seconds into each stage. Expired gases were continuously sampled and analysed using a Beckman Metabolic Measurement Cart (OM-11 oxygen analyser and...
Table 1  Three comparisons of the same women in an observational study (follicular, luteal) and during a randomised, placebo controlled trial of moderate dose triphasic oral contraceptive (Synchrophas) compared with the placebo group

<table>
<thead>
<tr>
<th></th>
<th>Oral contraceptive group</th>
<th>Placebo</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Follicular</td>
<td>Luteal</td>
<td>Treatment</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>60.2 (54.3 to 66.2)</td>
<td>60.6 (54.3 to 66.8)</td>
<td>61.2 (55.0 to 67.5)</td>
</tr>
<tr>
<td>Body fat (%)</td>
<td>16.5 (12.7 to 20.4)</td>
<td>16.9 (13.9 to 20.0)</td>
<td>17.5 (13.7 to 21.3)</td>
</tr>
<tr>
<td>Sum of skinfolds (mm)</td>
<td>38.5 (37.3 to 39.7)</td>
<td>39.2 (38.5 to 39.8)</td>
<td>37.8 (37.5 to 39.9)</td>
</tr>
<tr>
<td>Oestradiol (pmol/l)</td>
<td>138.7 (88.4 to 189.0)</td>
<td>442.1 (324.6 to 559.6)</td>
<td>347.6 (136.4 to 558.7)</td>
</tr>
<tr>
<td>Haemoglobin (g/l)</td>
<td>131.3 (126.7 to 135.9)</td>
<td>132.6 (128.6 to 136.5)</td>
<td>130.7 (126.9 to 134.5)</td>
</tr>
<tr>
<td>Sum of skinfolds (mm)</td>
<td>68.8 (55.7 to 81.9)</td>
<td>73.1 (59.9 to 86.4)</td>
<td>79.2 (63.6 to 94.8)</td>
</tr>
<tr>
<td>VO2MAX (l/min)</td>
<td>104.5 (96.6 to 112.4)</td>
<td>105.3 (97.3 to 113.2)</td>
<td>102.6 (93.7 to 103.2)</td>
</tr>
<tr>
<td>VO2MAX (ml/kg/min)</td>
<td>54.7 (51.6 to 57.9)</td>
<td>53.7 (51.0 to 56.5)</td>
<td>52.0 (49.0 to 55.1)</td>
</tr>
<tr>
<td>Maximal heart rate (bpm)</td>
<td>190.7 (181.8 to 199.7)</td>
<td>190.0 (180.7 to 199.3)</td>
<td>192.6 (181.9 to 203.1)</td>
</tr>
<tr>
<td>RER</td>
<td>1.17 (1.12 to 1.21)</td>
<td>1.16 (1.12 to 1.23)</td>
<td>1.16 (1.11 to 1.20)</td>
</tr>
<tr>
<td>Quadriceps peak torque (N.m)</td>
<td>158.1 (136.9 to 179.4)</td>
<td>153.1 (135.4 to 170.7)</td>
<td>145.1 (123.6 to 166.6)</td>
</tr>
<tr>
<td>Hematocrit max (N.m)</td>
<td>89.2 (72.0 to 106.4)</td>
<td>93.4 (79.5 to 107.3)</td>
<td>89.4 (75.6 to 103.2)</td>
</tr>
</tbody>
</table>

Values are mean (95% confidence interval).

*Significant time main effect (p<0.05).
**Significant group x time interaction (p<0.05).

AST, Anaerobic speed test; RER, respiratory exchange ratio; BTPS, body temperature and pressure saturated.

Isokinetic strength

Repeated measures analysis of variance was used to test for differences in isokinetic strength (Cybex II measurement of isokinetic strength) between different treatments, and to determine if any of these differences were significant.

Anaerobic performance

High intensity running performance was assessed, by the anaerobic speed test (AST). Participants rested for at least 1.5 hours before the VO2MAX test before measurement. After an adequate warm up, subjects were measured at VO2MAX. After VO2MAX, subjects performed the run at 8 mph (3.52 m/s) at a 20% incline until exhaustion (defined as the point at which the subject could no longer maintain the initial speed). Time (seconds) to fatigue was used as the performance index. The test-retest reliability of the AST was 0.76–0.91.)

Endurance performance

Endurance performance was assessed as the running time in endurance (time to exhaustion at 90% of VO2MAX). This workload was determined when subjects had reached 90% of predicted maximum heart rate, and when gas exchanges and room air after each test. A maximal test was defined as a plateau or decrease in VO2MAX despite an increase in workload. Resting heart rate was expressed as a percentage of the subject’s maximum heart rate. The subject completed the test with a respiratory exchange ratio of 1 to 1.1, attainment of at least 90% of predicted maximum heart rate, and end of test criteria: a plateau or decrease in VO2MAX despite an increase in workload.

1.2 carbon dioxide analyser (LSI,麻, 2002); and an 1.8 dilution system (Deuterium-4, 2002), determined

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contraceptive group across the three phases. In contrast, there = 0.019 respectively). Aerobic capacity decreased in the oral contraceptive and placebo groups over time (p = 0.050 and p

Both absolute and relative VO₂MAX differed between the oral contraceptive groups. Group differences were not significant (group treatment phase, but those in the placebo group showed no

data in the oral contraceptive group (group × phase, p>0.05). Change in sum of skinfolds was significantly different between the groups over time, with a larger increase in the oral contraceptive group (group × phase, p = 0.004; fig

Hormones and blood samples
As expected, oestradiol (p<0.01) and progesterone (p<0.01) values differed significantly between the follicular, luteal, and treatment tests for all subjects, but did not vary as a function of oral contraceptive treatment (table 1). Haemoglobin concentration, packed cell volume, and mean red cell volume did not differ significantly between groups over time, with a larger increase in the oral contraceptive group (group × phase, p = 0.050 and p

exercise performance
Aerobic capacity
Both absolute and relative VO₂MAX differed between the oral contraceptive and placebo groups over time (p = 0.050 and p = 0.019 respectively). Aerobic capacity decreased in the oral contraceptive group across the three phases. In contrast, there was a slight decrease in VO₂MAX between the follicular and luteal phase tests, but an increase in the third test in the placebo group. The mean decrease from the follicular to treatment phase was 4.7% in the oral contraceptive group compared with a 1.3% improvement with placebo. Figure 3 illustrates individual changes. There were no significant fluctuations in maximum minute ventilation (Ve), maximum heart rate, or maximum respiratory exchange ratio accompanying changes in VO₂MAX.

Endurance performance, anaerobic capacity, and strength
There were no significant differences in endurance performance (at 90% of VO₂MAX), anaerobic capacity (as measured by the AST), or isokinetic strength (on a Cybex II dynamometer) within or between groups over time (table 1).

DISCUSSION
To our knowledge, this is the first randomised, double blind, placebo controlled trial of the effects of oral contraceptive on indicators of athletic performance in highly trained women (VO₂MAX = 50 ml/kg/min). Use of moderate dose triphasic oral contraceptive resulted in a mean decrease in VO₂MAX of 4.7% in trained women compared with a 1.5% improvement with placebo. Although there was high individual variability in response to oral contraceptive administration, there was a clear trend towards a detriment in VO₂MAX in highly trained women taking oral contraceptive. The decrease in VO₂MAX was accompanied by an increase in sum of skinfolds, but not by significant changes in weight or measures of strength, anaerobic, or endurance performance.

Previous studies on the role of oral contraceptive on athletic performance have assessed a variety of performance indicators with varying protocols, duration and type of oral contraceptive use, and fitness levels of participants. Researchers have examined the effect of oral contraceptive on VO₂MAX, submaximal endurance performance, strength, anaerobic capacity, and side effects such as weight gain.

Maximal aerobic capacity
Studies in untrained or moderately trained women have shown mixed effects of oral contraceptive use on VO₂MAX. Daggett and colleagues showed a significant reduction in VO₂MAX (from 44.6 to 39.8 ml/kg/min) in a group of seven moderately trained women after one to two months of oral contraceptive use. Another study used a design similar to the present investigation, with both a control group (n = 6) and an oral contraceptive group (n = 6). Over six months, the control group increased aerobic capacity by about 8% (from 42.6 (2.8) to 45.9 (5.8) ml/kg/min), whereas after six months of monophasic oral contraceptive administration, VO₂MAX had decreased by about 7% (from 41.2 (11.8) to 38.4 (9.8) ml/kg/min). Changes were associated with a decrease in the oxygen pulse (12.1 (3.2) to 11.2 (2.2) ml per beat) and were reversible on discontinuation of treatment. The smaller differences in change in VO₂MAX in our study could be due to lower doses of exogenous steroids in the oral contraceptive, shorter duration of administration, or the greater fitness level of our participants. In contrast, other studies showed no effect of oral contraceptives on VO₂MAX in moderately trained women.

As in our study, the observed decreases in VO₂MAX have not been directly linked to significant alterations in O₂ carrying capacity of the blood (haemoglobin concentration or packed cell volume), or other physiological measurements influencing O₂ uptake or delivery to the tissue. Although the mechanisms are unclear, exogenous oestrogen may exert a deleterious effect on aerobic capacity. The changes are probably not due to progesterin. A well controlled, randomised, double blind, placebo controlled trial showed that high doses of medroxyprogesterone (20 mg three times/day for five doses) in men had no effect on VO₂MAX, but did increase minute ventilation as expected.

Submaximal endurance performance
Oral contraceptives have been shown to alter substrate metabolism, including carbohydrates and lipids, and to cause a decrease in blood glucose with heavy exercise. These

Figure 3 Percentage in VO₂MAX from follicular to treatment phase for women in the placebo and oral contraceptive groups.
It has been postulated that oral contraceptive use may prevent anaerobic capacity, which may be a different response to oral contraceptive use at lower hormone levels. This is in agreement with other short term studies. A randomised, double blind, placebo controlled study showed that oral contraceptive use may decrease aerobic capacity in some highly trained athletes, but there is high individual variability. Further study is needed to determine mechanisms of change and to document whether changes are reversible or persist with longer term use.

Strength and anaerobic capacity
It has been postulated that oral contraceptive use may prevent normal decreases in strength that occur during the luteal phase of a menstrual cycle. We saw no significant differences in measurements of muscle strength with oral contraceptive use or placebo. The overall effect of oral contraceptive on strength remains unknown.

We also saw no changes in anaerobic performance as a function of oral contraceptive use. Although few studies have been performed, there does not appear to be any effect of oral contraceptive on energy metabolism for short term anaerobic work. However, the scores for this test were relatively low in most of the athletes in our study, indicating a low anaerobic capacity. This is consistent with the fact that these subjects were well trained for predominantly aerobic-type activities. The effect of oral contraceptive use on anaerobic performance in highly trained anaerobic athletes should be explored.

Benefits and side effects of oral contraceptives
Potential benefits of oral contraceptive for athletic performance include decreased dysmenorrhoea, iron deficiency, and anaemia risks in women experiencing heavy flow. All participants had normal haemoglobin levels, and there were no significant oral contraceptive related changes in either haemoglobin or packed cell volume over six weeks. This is in agreement with other short term studies.

Early studies of high dose oral contraceptive formulations documented side effects, including fluid retention and weight gain. Biphasic and triphasic pills contain 30–40% lower levels of hormone and appear to have a corresponding decrease in adverse effects. In this study, athletes taking oral contraceptive had a non-significant weight gain of about 1 kg over six weeks compared with women in the placebo group. The significant increase in sum of skinfolds in the oral contraceptive group suggests that the weight increase was due primarily to an increase in subcutaneous body fat, although increased water retention cannot be excluded. Overall, recent non-controlled studies suggest no long term change in weight with oral contraceptive use, but changes in body composition have not been assessed.

Limitations
A caveat in this type of research (that only became evident during the course of the study) is the relative impossibility of carrying out true double blind studies with oral contraceptives. Approximately half of the participants were aware that they were taking oral contraceptives because of subtle changes, alterations in the pattern of their normal menstrual cycles, and the presence of side effects such as breakthrough bleeding throughout the cycle. Also, as noted, two of the seven women on the moderate dose oral contraceptive actually still showed hormonal evidence of ovulation.

Studies of this nature are also difficult to control because of the tremendous individual variability in timing of ovulation, response to oral contraceptive treatment, and cycle phase. Although we meticulously performed all treatment phase tests on days 14–17 of the menstrual cycle, there was a high degree of individual variability in the actual day of ovulation in the test cycle. Most women were actually in the mid- or late-follicular phase according to serum progesterone levels. However, two women in each group appeared to have ovulated before treatment tests. Results of our study were similar regardless of the phase with which data were compared. Nonetheless, the difficulty of repeating tests in the exact phase of the cycle over time should be noted.

Summary
The results of this study indicate that administration of this moderate dose triphasic oral contraceptive for two cycles does not have any apparent or measurable effect on most components of athletic performance in this group of elite women athletes. The small decreases in V\textsubscript{O}\text{MAX} that occurred in women taking oral contraceptive suggest that exogenous oestrogen may exert a deleterious effect on aerobic capacity with potential implications for elite performance. The magnitude of this effect varied between individuals. Further studies are necessary to delineate potential mechanisms of the change in functional aerobic capacity and body weight, and to further document whether changes in performance are reversible on discontinuation of treatment. Studies of the effects of oral contraceptive after longer term use (more than six months), and with larger sample size will also provide important insight into the effects of oral contraceptives on athletic performance. In addition, different formulations of oral contraceptive should be compared.

Authors’ NOTE
Since acceptance of our paper, we have learned that another group of authors has published similar findings from their work: Casazza GA, Sub S-H, Miller BF, et al. Effects of oral contraceptives on peak capacity. J Appl Physiol 2002; 93:1698–1702

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