Effects of Oral Contraceptive Use on Exercise Capacity in Female Elite Soccer Players

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Abstract

The purpose of this project was to assess the effects of oral contraceptives (OC) on exercise capacity in female elite soccer players. Fourteen subjects (N=7 oral contraceptives users (OCU) + 7 non-OCU (N-OCU)) were recruited. An assessment of body composition was determined by Dual energy X ray absorptiometry and endogenous ovarian hormone concentrations in serum measured. A maximal treadmill test was performed to assess VO\textsubscript{2} peak, VCO\textsubscript{2}, blood glucose and blood lactate levels during exercise. The endogenous ovarian hormone concentrations were significantly lower among the OCU. After exercise testing OCU had significantly lower VO\textsubscript{2} peak when normalised to total body weight or muscle mass, compared to the N-OCU. OCU had higher respiratory exchange ratio (RER) during submaximal exercise, indicating altered substrate utilization. The OCU had significant lower capillary blood glucose concentrations after exercise. The main finding of our study was that peak oxygen uptake was lower in female elite soccer players using OC than N-OCU, whether it is normalized to body weight or muscle mass. The difference appears to be related to effects on skeletal muscle metabolism.

Keywords: Blood Glucose; Respiratory Exchange Ratio; Body Composition; VO\textsubscript{2} peak; Muscle Mass

Introduction

Estrogen in physiological concentrations is beneficial for oxidation, primarily oxidation of fats [1]. Estrogen also facilitates lipolysis and the storage of glycolgen, while it inhibits glycogenesis and glycolysis [1,2]. Synthetic estrogen analogs also alter glucose and lipid metabolism, and estrogen in un-physiologically high or low concentrations alters glucose flux via higher levels of insulin and a glucagon redundancy [3]. These levels of estrogen decrease the insulin sensitivity, indicating a metabolic inflexibility similar to the metabolic syndrome [2,4,5].

Oral contraceptives (OC) are used by 80% of female elite athletes [6] for reasons such as birth control, cycle regulation and treatment of dysmenorrhea or amenorrhea [7]. The OC appear in various forms such as combination (with estrogen and progesterone) or progesterone only, with the progesterone used in several forms. Estrogen is only included in one form where these pills are taken over a 28-day cycle including a seven day withdrawal [8,9]. The combined OC come as monophasic, biphasic or triphasic pills depending on the variation in concentration of the progesterone and estrogen distributed over the 28-day cycle [10]. The progesterone and estrogen in the pills suppress the production of endogenous progesterone and estrogen, except during the 7-day withdrawal period, when the endogenous es-
Isoprogestin level increases abruptly [9]. Relative to the untreated state, the levels of exogenous estrogen are three to five times higher than the endogenous levels during a normal menstrual cycle, while the exogenous levels of progesterone are about one to two times higher than the endogenous levels [7]. As non-physiological levels of estrogen may cause metabolic inflexibility, similar to the metabolic syndrome [2,4,5], OC may therefore influence the metabolism in high performance female athletes.

Studies on the effect of OC on athletic performance show conflicting results - probably due to small sample sizes, athletes with different training status, different exercise protocols and different OC [8,9]. But when summarizing published studies, it seems as if OC may influence aerobic capacity, anaerobic capacity, anaerobic power and reactive strength [9]. There are also a few studies that have evaluated the effect of OC on body composition and its relation to exercise capacity [11,12]. Lloyd et al. [11] found no effect of OC on body composition in teenage female athletes - similar to the findings in untrained controls as reported by Rickenlund et al. [12]. In contrast, in endurance athletes OC were associated with higher fat mass than expected, even though the aerobic capacity was not affected [12]. This implies that OC may exert different effects on body composition according to training status.

With this background, we performed a study where we hypothesized that OC may affect aerobic capacity, substrate utilization and body composition in highly elite female soccer players.

**Methods**

**Subjects**

Fourteen elite female soccer players from a team playing at the highest league voluntarily participated in the study. Seven used oral contraceptives (OCU) prior to inclusion in the study. Six subjects used

1. Monophasic OC: of whom four used 20-35µg ethinylestradiol combined with 150µg levonorgestrel, one used 250µg norgestamin and one used 150 desogestrel.

2. One subject used triphasic OC: with 30-40µg ethinylestradiol and 50-125µg levonorgestrel.

All subjects provided written informed consent prior to their inclusion and the study was approved by the regional ethical review board in Lund, Sweden.

**Experimental design**

The design of this study was cross-sectional. There were two laboratory visits. At the first visit, a history was taken including use of OC and menstrual cycle. A venous blood sample was obtained for measurements of estrogen and LH, analyzed with one step and two step immunometric method ElectrChemiluminescenceImmunoassay (ECLI).

All subjects then performed an incremental exercise test to exhaustion. The second visit occurred within one to three days when a full body dual energy X-ray absorptiometry (DXA) scan was performed for determination of body composition.

**Exercise Test**

A maximal treadmill exercise test was performed to determine VO$_2$peak. The exercise test started at 8 km/h, 0º incline, for two minutes, whereafter the speed increased to 10 km/h for another two minutes, to 11 km/h for 1 minute, and to 12 km/h for one minute. Thereafter, the slope increased by 1º per minute until exhaustion. Respiratory gas exchange and pulmonary ventilation were measured breath-by-breath (Oxycon Mobile, Jeager, Hoechberg, Germany). Heart rate (HR) was monitored continuously at 5-s intervals during the test (Polar T 61, POLAR, Oulu, Finland). A single-plane (vertical) accelerometer (Manufacturing Technology Incorporated, Fort Walton beach, FI, USA), model 7164, placed over the fifth lumbar vertebra (L5) attached with a rubber band around the waist was used [10]. The subjects were verbally encouraged to exercise as hard as possible. The Oxycon Mobile system was validated against measurements with Douglas bags and repeated measurements have been performed showing a coefficient of variance for VO$_2$ of 3% [13-16]. Calibration of the gas sensors was performed before each test with a certified gas mixture. Air flow was calibrated before each test using a calibration syringe.

**Blood sampling and analysis**

Two capillary blood samples were taken in a rested state for analysis of hemoglobin (HemoCue, Ängelholm, Sweden) content before the
exercise test. Two capillary blood samples were taken in a rested state before the exercise test and two and five minutes after abortion of the test for analysis of blood glucose (HemoCue, Ängelholm, Sweden). Blood lactate (Dr Lange, Germany) from capillary blood was determined before the exercise test and two and five minutes after abortion of the test.

**Body composition**

Muscle mass and fat mass were measured by dual energy X ray absorptiometry (DXA) in total body (TB), arms, legs and trunk by a TB scan, with the subject scanned in supine position as previously described. Daily calibration of the machines with the Lunar phantom took place during the entire study period. The coefficient of variation (CV), evaluated by duplicate measurements in 14 healthy adults, was for TB fat mass 4.1% and TB lean mass 0.6%. The measurements and analyses were all performed by one research technician. Body weight was measured with a standard weigh scale to the nearest 0.1 kg and body height by a stadiometer to the nearest 0.5 cm. Body mass index (BMI, kg/m²) was calculated as weight in kilograms divided by height in meters squared. The measurements were carried out at the same time as the DXA measurements.

**Data analysis**

**Exercise capacity**

The absolute VO₂peak was defined as the highest recorded value during the last minute of the test. Oxygen uptake reached a plateau and the respiratory exchange ratio (VCO₂/VO₂) exceeded 1.10 in all subjects.

Vertical displacement was assessed with a one-dimensional accelerometer during the incremental exercise test, one second epoch was recorded. Vertical displacement was calculated as the average number of counts during horizontal running and slope running.

**Statistics**

Values throughout are given as median and range. Mann-Whitney’s U-test was used when comparing the groups. Effect size was calculated as (meanN-OCU-meanOCU)/ standard deviationN-OUC. Spearman’s correlation coefficient (r) was used to analyze interrelationships between variables. SPSS (Version 17.0, SPSS Inc. Chicago, Illinois, USA) was used for the statistical analyses. The p<0.05 criterion was used for establishing statistical significance.

**Results**

Subject characteristics are shown in Table 1. There was no difference between groups in height (p=0.54), weight (p=0.46), BMI (p=1.0), muscle mass (p=0.53; effect size 0.2) or fat mass (p=0.23; effect size 0.6).

<table>
<thead>
<tr>
<th></th>
<th>N-OCU (n=7)</th>
<th>OCU (n=7)</th>
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<tbody>
<tr>
<td>Age (yr)</td>
<td>25 (20-32)</td>
<td>24 (18-30)</td>
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<tr>
<td>Height (cm)</td>
<td>170 (164-178)</td>
<td>171 (167-178)</td>
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<tr>
<td>Weight (kg)</td>
<td>62.7 (53.2-78.0)</td>
<td>63.5 (52.0-56.6)</td>
</tr>
<tr>
<td>BMI (kg m²)</td>
<td>22.6 (19.5-24.6)</td>
<td>22.1 (20.8-25.6)</td>
</tr>
<tr>
<td>Fat mass (kg)</td>
<td>12.5 (9.2-17.2)</td>
<td>13.5 (11.2-16.7)</td>
</tr>
<tr>
<td>Muscle mass (kg)</td>
<td>48.6 (40.2-57.0)</td>
<td>45.9 (43.7-57.3)</td>
</tr>
<tr>
<td>Fat mass (%)</td>
<td>20 (15-22)</td>
<td>22.5 (18-27)</td>
</tr>
<tr>
<td>Muscle mass (%)</td>
<td>75 (73-80)</td>
<td>73 (69-77)</td>
</tr>
<tr>
<td>Day of cycle</td>
<td>14 (1-29)</td>
<td>3 (1-18)</td>
</tr>
<tr>
<td>Estrogen (pg ml⁻¹)</td>
<td>472 (279-1450)</td>
<td>125 (125-146)</td>
</tr>
<tr>
<td>LH (pg ml⁻¹)</td>
<td>5.2 (2.0-17.8)</td>
<td>3.2 (1.3-5.7)</td>
</tr>
<tr>
<td>Hemoglobin (g l⁻¹)</td>
<td>127 (118-137)</td>
<td>132 (122-150)</td>
</tr>
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N-OCU=Non-oral contraceptive user; OCU=Oral contraceptive user; LH =luteinizing hormone

There were no statistical significant difference between groups as determined with Mann-Whitney’s U-test.
In contrast there were group differences in endogenous ovarian hormone concentrations, estrogen (p=0.001), but not between day of the menstrual cycle and hemoglobin (p=0.13) concentration (Table 1). $\text{VO}_2\text{peak}$ was lower in OCU than in non-OCU (N-OCU), irrespective if $\text{VO}_2\text{peak}$ was normalized to body weight (p=0.01) or muscle mass (p=0.004) (Table 2). There were no differences in peak respiratory exchange ratio (RER$_{\text{peak}}$) (p=0.38), peak heart rate (HR$_{\text{peak}}$) (p=0.53) or ventilation (VE$_{\text{peak}}$) (p=0.81) (Table 2) between investigated groups.

During sub-maximal exercise there were group differences in RER at 12 km 0° slope (p=0.026), 12 km 1° slope (p=0.053) and 12 km 2° slope (p=0.017) (Figure 1).

There were also differences in capillary blood glucose concentrations after exercise both at two (p=0.007) and five minutes (p=0.004) but no differences in capillary blood lactate levels after exercise (p=0.71 and p=0.37 for 2 and 5 minutes, respectively) (Table 3).

Muscle mass correlated with $\text{VO}_2\text{peak}$ ($\rho = 0.91; p<0.001$).
The main finding in our study was that there was a significant difference in maximal oxygen uptake normalized to body weight between OCU and N-OCU. We found no differences between groups in physical characteristics or body composition, and these factors can thus not explain the difference in oxygen uptake in our study. The difference in maximal oxygen uptake remained significant between the groups when normalized to muscle mass, further indicating that the possible effects of OC are not mediated through changes in body composition.

Endogenous estrogen was, as expected, significantly lower in the OCU group (Table 1). The levels of exogenous estrogen are three to five times the endogenous levels during a normal menstrual cycle while the exogenous levels of progesterone is about one to two times the untreated state [7].

There was no significant group difference in absolute $\text{VO}_{2\text{peak}}$, while a difference emerged when $\text{VO}_{2\text{peak}}$ was normalized to body weight or muscle mass. Skeletal muscle is, as illustrated by the close correlation between muscle mass and $\text{VO}_{2\text{peak}}$, the main site of oxygen consumption during exercise and should be the most relevant normalization. Hansen et al [18] have described that OC may have a negative effect on the net myofibrillar protein balance, suppressing the net increase of muscle mass due to training, which may affect oxygen consumption adjusted for muscle mass. The $\text{VO}_{2\text{peak}}$ kg$^{-1}$ muscle mass in the OCU using group was 10% lower than in the N-OCU (Table 2), a difference of biological significance in elite soccer players [19]. This indicates a difference in muscle metabolic economy/efficiency rather than muscle mass. OCU did the same amount of work (Table 1) as the N-OCU, but used less oxygen to do it. The answer could lie in substrate utilization, with the difference between the groups being that OCU metabolized more CHO, which produces more energy per oxygen molecule than metabolizing fats – as indicated by the higher submaximal RER seen in OCU.

Measurement of peak oxygen uptake requires maximal effort from the test subject. $\text{HR}_{\text{peak}}$ as well as $\text{RER}_{\text{peak}}$ were very similar in the two groups, indicating that the difference in oxygen uptake cannot be explained by different effort. The group similarity in vertical displacement also supports this notion. During sub-maximal exercise, RER was higher in OCU than in N-OCU, suggesting differences in substrate utilization, using more carbohydrates (CHO). We also found lower blood glucose in the OCU than in the N-OCU group after exercise. This agrees with Bemben et al., [20] who found significantly lower blood glucose during sub-maximal exercise in OCU, indicating either lower release of glucose from the liver or higher extraction in the skeletal muscles. Suh et al., [5] described a decrease in glucose flux in OCU but not carbohydrate oxidation during moderate-intensity exercise, but the participants in that study were moderately active rather than elite athletes. This difference may be relevant, as training status has been shown to affect substrate utilization in skeletal muscle [21].

There are important limitations of this study. One is the parallel group design. Another limitation is that the measurements were not standardized with respect to menstrual cycle phase. This may not be a major drawback, since most studies have shown exercise capacity to be unaffected by menstrual phase [22]. A further limitation is the limited number of subjects, which may have under power the findings. On the other hand, the subjects were recruited from a single team of elite professional soccer players. Variations in fitness levels, training history and habits, diet, and so on, are therefore likely to be lower than if players from outside the team were also included in the study.

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<tr>
<td>Glucose $\text{rest (mmol)}$</td>
<td>5.3 (4.5-6.6)</td>
<td>5.2 (1.0-5.8)</td>
</tr>
<tr>
<td>Glucose $\text{2 minutes (mmol)}$</td>
<td>9.5 (8.2-10.5)</td>
<td>7.3 (1.7-9.5) $^{0.007}$</td>
</tr>
<tr>
<td>Glucose $\text{5 minutes (mmol)}$</td>
<td>9.1 (8.3-10.1)</td>
<td>7.5 (6.5-8.9) $^{0.004}$</td>
</tr>
<tr>
<td>Lactate $\text{rest (mmol)}$</td>
<td>3.4 (1.5-6.7)</td>
<td>1.2 (1.0-3.0) $^{0.02}$</td>
</tr>
<tr>
<td>Lactate $\text{2 minutes (mmol)}$</td>
<td>7.7 (6.1-11.7)</td>
<td>8.1 (5.9-9.0)</td>
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<tr>
<td>Lactate $\text{5 minutes (mmol)}$</td>
<td>7.2 (5.9-11.4)</td>
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N-OCU=Non-oral contraceptive user OCU= Oral contraceptive user

Statistical difference between groups was determined with Mann-Whitney’s U-test

Table 3. Capillary blood glucose and capillary blood lactate at before the maximal exercise test and two and five minutes after the maximal exercise test (median with ranges within brackets).

**Discussion**

The main finding in our study was that there was a significant difference in maximal oxygen uptake normalized to body weight between OCU and N-OCU. We found no differences between groups in physical characteristics or body composition, and these factors can thus not explain the difference in oxygen uptake in our study. The difference in maximal oxygen uptake remained significant between the groups when normalized to muscle mass, further indicating that the possible effects of OC are not mediated through changes in body composition.

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Conclusion

This study indicates female elite soccer players that use OC may have a lower aerobic capacity than N-OCU due to a mechanism that include altered substrate utilization in skeletal muscle. As this may influence the performance, female elite athletes should take this into account when deciding on taking OC.

Acknowledgments

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References


