Do Oral Contraceptives Alter Knee Ligament Damage with Heavy Exercise?

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Hormones such as estradiol have an effect on human connective tissue, making women more susceptible to knee injuries. Indeed, women have a greater risk for non-contact injuries of anterior cruciate ligament (ACL) compared to men when participating in the same sports. The purpose of the present study was to examine the difference in ACL laxity after an eccentric exercise in the lower limbs in young healthy women between oral contraceptive pill (OCP) users and non-OCP users to see the effect of OCP on ACL laxity. Forty young healthy women participated in the experiments (25 with normal menstrual cycle and 15 with taking OCP). ACL laxity and a visual analog pain scale were measured before and after a bout of squat. OCP users had more pain than non-OCP users after heavy exercise ($p < 0.001$). Both groups showed a significant reduction in ACL laxity on the 2nd day after exercise ($p < 0.05$). While ACL laxity was always less in the OCP group, when expressed as a percent change from baseline, the ACL laxity change was similar in both groups ($p > 0.05$). We found that there was no statistically significant difference in ACL laxity recovery over time in response to the delayed onset muscle soreness after a bout of squat between two groups. However, health professionals working with young female adults should recognize that OCP users with less ACL laxity are at higher risk for having knee injuries because of ACL stiffness when doing exercise.

Keywords: anterior cruciate ligament laxity; eccentric exercise; menstrual cycle; oral contraceptive pills; women
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Introduction

The effect of estrogen on musculoskeletal connective tissue is well known (Liu et al. 1997; Arendt et al. 1999; Yu et al. 1999; Zazulak et al. 2006; Park et al. 2009a). It has been determined that 17-*β* estradiol receptors exist in human connective tissue. Women have a greater risk for non-contact injuries of anterior cruciate ligament (ACL) compared to men (Zazulak et al. 2006). Many studies have investigated if steroid hormones make women more susceptible to knee injuries (Arendt et al. 1999; Griffin et al. 2000; Zazulak et al. 2006; Park et al. 2009a, b; Lee et al. 2014). One hormone in particular, estradiol, seems to play an important role in protecting women from muscle and ligament damage (Thompson et al. 1997; Savage and Clarkson 2002).

According to National Health Statistics Report, oral contraceptive pills (OCP) are the most common method used by women in their teens and 20s (Jones et al. 2012) for contraception. It is used for not only contraceptive purposes, but 14% of women have used OCP for non-contraceptive purposes (Kenny et al. 2008). There have been numerous studies investigating the effects of OCP on the body because the number of women using OCP has constantly increased. The combined OCP contains estrogen and progesterone as synthetic steroids that prevent ovulation by inhibiting the release of follicle-stimulating hormone and luteinizing hormone from the pituitary gland in the brain (Kenny et al. 2008; Krishnan and Kiley 2010). The 17-*β* estradiol receptors on the ACL are well established and therefore, it is of no surprise that OCP users have less ACL laxity than non-OCP users due to consistently lower levels of estradiol (Martineau et al. 2004; Lee et al. 2014).

Previous studies have demonstrated that women have more damage to the quadriceps muscle and a greater reduction in ACL laxity compared to men as a result of delayed onset muscle soreness (DOMS) after high-intensity lower body exercise (Lee et al. 2013). There is an obvious sex-difference in the role of estrogen in regulating muscle mass and ligament laxity (Lee et al. 2013). Since estrogen levels are lower in OCP users, there might also be a difference in

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muscle soreness and ACL ligament damage and recovery with intense lower body exercise. Thus, the present study tested the difference in ACL laxity following a bout of squat exercise in the lower limbs in young healthy women between OCP users and non-OCP users.

Methods

Participants

Forty women participated in the study. Twenty five participants were women with a regular menstrual cycle and 15 participants were women who are taking OCP. Participants were recruited from Loma Linda University and the surrounding community. They were recruited using several methods. Study flyers were placed on the main bulletin board of the School of Allied Health Professions and Public Health in Loma Linda University. This flyer was also sent via email to all faculty and students in the School of Allied Health Professions. The general characteristics of the participants are listed in Table 1.

Participants were 18 to 30 years of age with a body mass index (BMI) between 15 and 30 who had a regular menstrual cycle or currently were using OCP (30 to 50 μg ethinyl estradiol) for at least one year. All women were healthy nonsmokers and had a low to moderate self-reported physical activity level. DOMS after exercise requires an increase in activity above normal levels found in daily living. Therefore, participants were excluded if they exercised their legs more than 2 days per week. In previous studies, this exclusion criteria has been effective in generating mild DOMS (Lee et al. 2013; Petrofsky et al. 2013). No one had cardiovascular disease, hepatic disease, diabetes, lower limb neuropathies, movement disorders, recent lower limb injuries or were taking any medication would affect sex hormones other than OCPs. The study was approved by the Institutional Review Board of Loma Linda University and all participants signed a statement of informed consent.

Procedures

OCP users were screened by questionnaire, which included questions regarding brand name, type, and the length of taking OCP. On the first day, before beginning the testing, height, weight, BMI were measured. Upon arriving at the laboratory, participants relaxed in a thermally neutral room temperature at 22°C for 20 minutes to stabilize their body temperature in a neutral environment. All measurements were collected on the 1st day as baseline data, squat exercise was accomplished on the 2nd day of the study and then measurements were taken again on 3rd day, 4th day, and 5th day of the study.

Outcome measures

Subjective pain scale: Subjective pain was measure by a visual analog scale (VAS). VAS is a 10 centimeter (cm) line with marked points at 0 and 10 cm where 0 indicated 'pain of free' and10 indicated 'very, very painful'. The subject was asked to place a vertical slash across the line to signify their level of knee pain. This scale has been established as a reliable and valid subjective outcome measure to assess acute and chronic pain (Carlsson 1983; Langley and Sheppeard 1985; Flandry et al. 1991).

Anterior cruciate ligament (ACL) laxity: ACL laxity was measured by anterior tibial displacement (ATD). A KT-2000 knee arthrometer (MEDmetric Corp, San Diego, California) was used to measure ATD. This validated device has been used for both clinical and basic research for the last decades (Kowalk et al. 1993; Werlich et al. 1993; Zazulak et al. 2006; Andrea et al. 2014; Kim et al. 2014). Participants were asked to lay supine in a predetermined position with 25 degrees of knee flexion. The process was accomplished by supporting both limbs with a firm, comfortable platform placed proximal to the popliteal space, which helped the subject to keep the knee flexed during the test. A foot positioning device and a thigh strap were used to prevent external rotation of the hip when necessary. The force necessary to generate an anterior glide of the proximal end of the tibia on the femoral condyles was measured with a strain gauge bridge arranged as a load cell. Force was applied to the ACL at 15, 20 and 30 lbs, force reported in this study was only at 30 lbs. As force was applied, the force and measured displacement were plotted on an x-y plotter to record the ligament laxity. A vernier caliper was used to measure ATD on the graph. One physical therapist with 5-years of experience and 3 years using this device performed the measurement of the ACL laxity for consistency on all participants.

Exercise protocols

All participants performed 15-minutes of squats. A squat involved standing erect and then flexing the hip just beyond 90 degrees (and the knee angle as appropriate) with the back held vertically. Participants were asked to complete squats for 5 minutes and then rest 3 minutes. This was repeated the 3 times.

Statistical analyses

Data was analyzed using SPSS for Windows version 22.0. Characteristics of the participants were summarized using means and standard deviations (SD). The distribution of the quantitative variables was examined using a One-Sample Kolmogorov-Smirnov Test. An independent t-test was used to compare general characteristics and baseline ACL laxity between the two groups. A mixed factorial analysis of variance was conducted to compare the subjective pain scale

Table 1. Means ± SD of general characteristics in each group (N = 40).

	Non-OCP users (n = 25)	OCP users (n = 15)	p value*
Age (years)	25.2 (1.6)	25.1 (2.8)	0.47
Height (cm)	163.5 (6.1)	162.3 (5.8)	0.27
Weight (kg)	58.4 (7.6)	59.0 (9.5)	0.41
BMI (kg/m^2)	21.9 (2.9)	22.3 (2.6)	0.32
Baseline ATD (mm)	5.3 (1.0)	4.5 (0.6)	0.01

ATD, anterior tibial displacement.
*Independent t-test.

and ACL laxity between the two groups over time. The Least Significant Difference (LSD) pairwise comparisons test for multiple comparisons was used to compare means of variables between any two different testing times. The level of significance was set at alpha (α) less than 0.05. Effect sizes were calculated to account for group variability. A post power analysis with an effect size of 0.12 according to the changes in ACL laxity with controlling baseline ACL laxity between the groups and a sample size of 40 indicated that the power was 82% with an alpha level of 0.05.

Results

Subjective pain scale

A subjective pain scale was measured using VAS (Vecchiet et al. 1983). VAS was not significantly different between OCP users and non-OCP users at baseline (0.16 ± 0.07 vs. 0.06 ± 0.08, p = 0.24, Fig. 1). Both groups showed a significant increase in pain after exercise. OCP users showed significantly higher pain compared to non-OCP users after exercise (p = 0.008). The pain peaked by the 1st day post-exercise in non-OCP users and the 2nd day post-

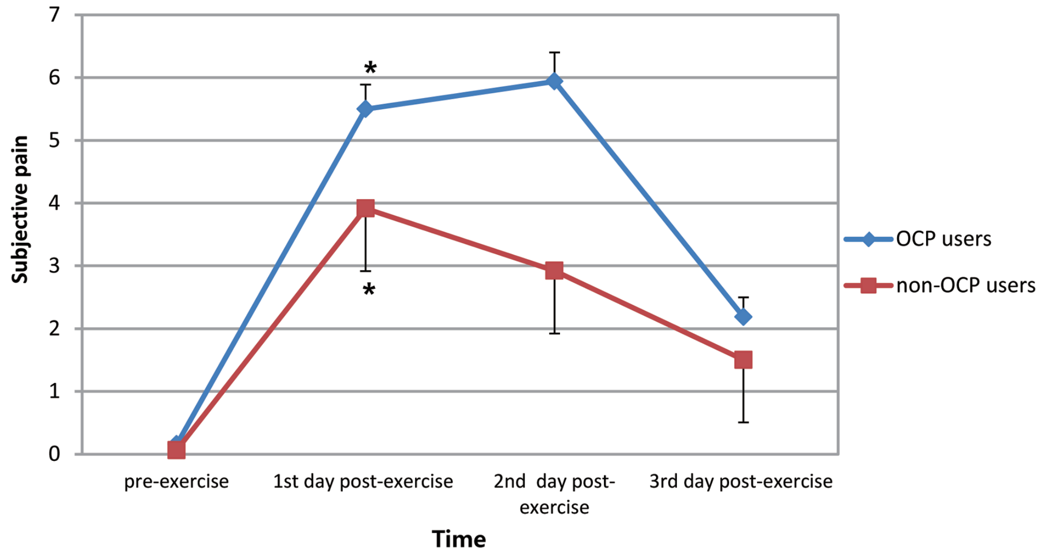

Fig. 1. Visual analog pain scale at pre- and post-exercise.
Mean ± SD of visual analog pain scale at pre-exercise (rest) and 1st, 2nd and 3rd days post-exercise in OCP users and non-OCP users.
*Significant difference in subjective pain between pre-exercise and 1st day post-exercise.

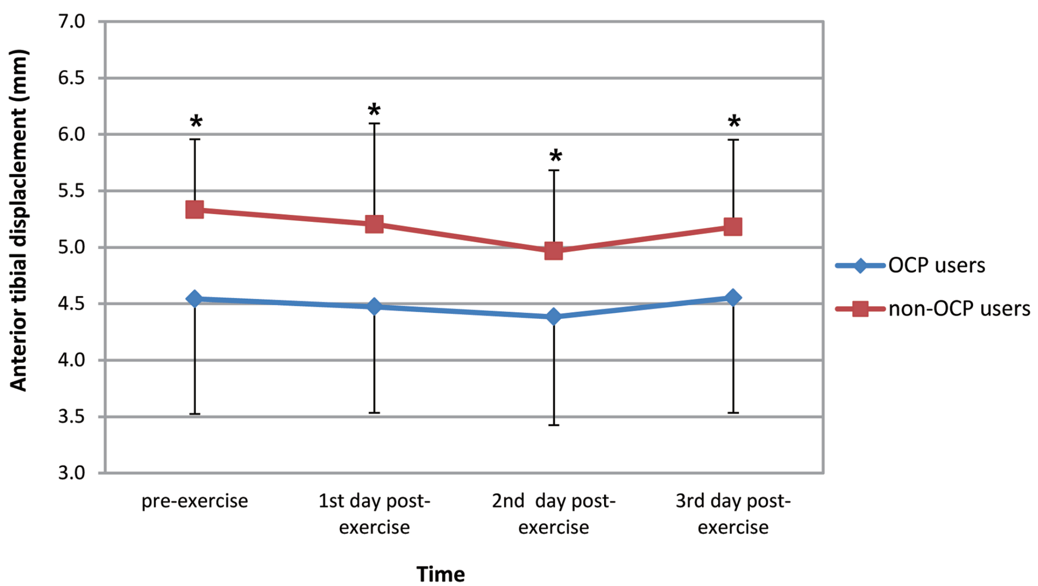

Fig. 2. Anterior tibial displacement at pre- and post-exercise.
Mean ± SD of anterior tibial displacement (ATD) measured at pre-exercise (rest) and 1st, 2nd and 3rd days post-exercise in non-OCP users and OCP users.
*Significant difference in ATD between OCP and non-OCP users.

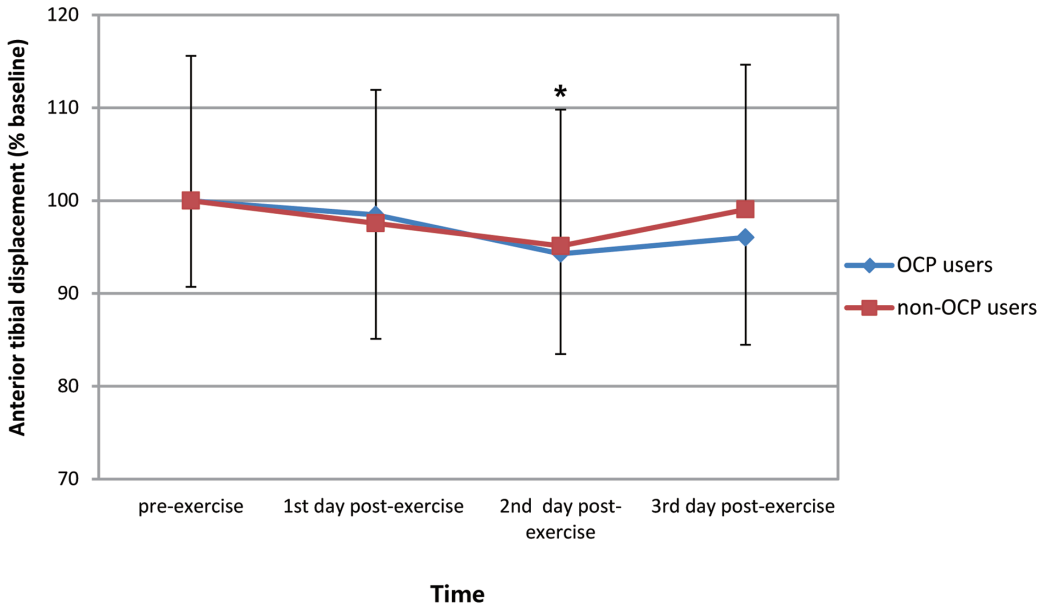

Fig. 3. % Change in anterior tibial displacement at pre- and post-exercise.
Mean ± SD of % change in anterior tibial displacement (ATD) measured at pre-exercise (rest) and 1st, 2nd and 3rd days post-exercise in non-OCP users and OCP users.
*Significant difference in ATD between pre-exercise and 2nd day post-exercise.

exercise in OCP users. However, there was no significant difference in VAS between the 2nd day and 3rd day post-exercise in both groups ($p > 0.05$).

Anterior cruciate ligament laxity

ACL laxity was measured by ATD. The results of the ATD changes in four different phases between non-OCP users and OCP users are shown in Fig. 2. A lower ATD value means less laxity of the ACL. ATD was significantly lower in OCP users compared to non-OCP users at baseline (4.54 ± 0.62 vs. 5.33 ± 1.04, $p = 0.01$, Table 1, Fig. 2). There was also lower ATD after the exercise in all participants with the lowest values in the OCP users. However, when expressed as a percent change in ACL laxity of the first day's ATD (Fig. 3), there were no significant changes in ATD over time ($p = 0.14$). We conducted post hoc comparison using LSD pairwise comparisons over time. Among all participants, there was a significant drop in mean ATD on the 2nd day after exercise compared to pre-exercise ($p = 0.02$, Fig. 2). There was no interaction between time and group ($p = 0.72$). However, there was a significant difference on a percent change of ATD between the two groups over time ($p < 0.05$).

Discusion

Previous studies have investigated the effects of OCP on muscle damage following heavy exercise. Even though the evidence that estrogen plays an important role in protecting muscle in humans has been well documented, there has been controversy on the result of the effects of OCP on muscle damage following heavy exercise (Thompson et al. 1997; Savage and Clarkson 2002; Ekenros et al. 2013). However, no one has looked at changes in ligament laxity after heavy exercise in relation to the effect of estrogen. There has been a common theory that the presence of 17-beta estradiol receptors in the ACL is related to ACL laxity at ovulation (Liu et al. 1997; Yu et al. 1999; Hansen et al. 2009; Lee et al. 2014). Therefore, the present study attempted to see the difference in pain scale and ACL laxity recovery following a bout of squat.

In terms of the subjective pain scale, there was a significant difference between the two groups over time after intense exercise. The results of the present study agree with previous investigations (Park et al. 2009a; Lee et al. 2014). OCP users had significantly more pain than non-OCP users after intense exercise in the lower limbs but the pattern was a little different. The pain peaked by the 1st day post-exercise in non-OCP users and 2nd day post-exercise in OCP users.

Interestingly, the results of ACL laxity were different. The present investigation found that women using OCP had significantly less ACL laxity compared to those who had a regular menstrual cycle before and after intense exercise. Since baseline ACL laxity between OCP users and non-OCP users was significantly different, we looked at a percent change of ACL laxity over time. The data showed that while both groups had a reduction in ACL laxness after heavy exercise, the relative percent change was the same for both groups. Both OCP users and non-OCP users showed significant reduction in ACL laxity on the 2nd day after exercise but no recovery following heavy exercise was found. This is probably due to poor blood supply in the ACL. Ligaments have poor circulation so they are more easily injured and the ability for the ligament to heal is limited (Arnoczky et al. 1979; Arnold et al. 1979; Cabaud et al. 1979).

This investigation examined ACL laxity after heavy exercise to compare women who were chronic OCP users for at least one year to those who had never used exogenous hormones. However, our study was limited by not measuring the estrogen serum concentration. Self-reported information was used only to determine the groups. Also, we did not recognize the phases of menstrual cycle in non-OCP users even though estrogen concentration level fluctuates during the menstrual cycle. Many researchers have shown that ACL laxity is significantly greater during ovulation than the follicular phase due to differences in the plasma estrogen concentration (Arendt et al. 1999; Park et al. 2009a).

In conclusion, prolonged use of OCP showed less ACL laxity compared to non-OCP users before and after heavy exercise. However, there was no statistically significant difference in ACL laxity changes between women with prolonged use of OCP and non-OCP users (women with a regular menstrual cycle) in response to the DOMS after intense exercise. No significant effect of prolonged use of OCP on ACL laxity changes after intense eccentric exercise was detected but more research is needed with longer periods recovery time to determine whether OCP has effects on ligament recovery after heavy exercise.

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Conflict of Interest

The authors declare no conflict of interest.

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