Do Combined Oral Contraceptives Protect Against Anterior Cruciate Ligament Injuries in Female Athletes?

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PROTOCOL SUMMARY

Purpose and Knowledge to be Gained	• The purpose of this study is to investigate the impact of combined oral contraceptive (COC) use on serum relaxin levels, ACL laxity, and rate of ligamentous injury among collegiate female athletes • Previous research suggests COC use may decrease serum relaxin levels, which could decrease ACL laxity and potentially protect against ACL injury (which is disproportionately higher in female athletes vs male athletes)
Research Procedures	• Assessment of baseline contraceptive status and initiation of study COC if participant desires • Participants will undergo the following assessments at baseline and at the four-month time point (1) Serum relaxin level (2) Knee joint anterior and posterior laxity will be tested using a KT-2000 arthrometer (Medmetric Corp, San Diego, CA) (3) Motion Tracking Analysis (4) Reported knee injury during study time period
Subject Population	• 150 female collegiate athletes competing in sports considered high-risk for ACL tears (basketball, soccer, and volleyball) • Recruited from surrounding universities (Loyola Marymount, Pepperdine) where Cedars-Sinai Kerlan Jobe-affiliated orthopedic surgeons practice • Participants who want to remain on no hormonal contraception or want to take study COC
Duration	• The study includes 2 in-person visits and one phone follow-up. • The total study duration is 12 months

GENERAL INFORMATION

CSMC Co-Investigators	**Natasha Schimmoeller MD, Melodie Metzger PhD**
Sponsor/Funder	Internal Funding
Collaborating Institutions Involved in the Research	None

1.0 BACKGROUND, RATIONALE

Increased female athletic participation was set forth after the establishment of Title IX.[11] With this increase in activity came a dramatic rise in ACL injuries, revealing a significant gender disparity with women having a 2-to-10 times greater risk of ACL rupture.[9] While numerous studies have revealed anatomic, neuromuscular and hormonal differences play a role,[3, 6, 7] one question that has not fully been addressed is the possible protective role of combined oral contraceptives (COCs).

Prevalence of COC use among female athletes has been estimated at 40% to 50%, showing a significant acceptance of COC use by many female athletes.[2, 12] Previous literature suggests that fluctuating hormones not only play a role is weakening the structure of the female ACL but also increase knee joint laxity, leading to poorer lower extremity biomechanics during sports and activities.[5, 6] While some risk factors are not modifiable, such as the size of a woman's ACL or femoral notch, the ability to safely alter a female's hormonal profile to confer a more protective, favorable environment may theoretically provide a viable intervention for the female athletic community in ACL injury prevention as well as in post-ACL reconstruction rehabilitation.

Thus, advancing our knowledge of the underlying pathophysiological mechanisms of ACL injuries will further the development of prevention, rehabilitation and training strategies to reduce the risk of sport-related injury, thereby enhancing the beneficial effects of physical activity on women's health for all ages. With 4 out of 5 heterosexually active women in the U.S. using COC in their lifetime, this research may also contribute to growing evidence of non-contraceptive benefits of COCs.

2.0 STUDY OBJECTIVES

We plan to investigate the hypothesis that combined oral contraceptives (COCs) reduce serum relaxin levels and ligament laxity in collegiate female athletes. Though this study cannot prove causality, we will also observe if rate of ligamentous injury in female athletes is reduced among women taking COC. Our specific aims are as follows:

Aim 1: To evaluate relaxin levels in female athletes on COC or no hormonal contraceptive

Aim 2: To quantify anterior and coronal plane (varus/valgus) knee laxity between female athletes using combined oral contraceptives and those who are not using any hormonal treatment.

Aim 3: To track the rate of ACL and other ligamentous injuries (ruptures / sprains) among female athletes and determine if COCs have a protective effect.

3.0 STUDY POPULATION

3.1 Selection of the Study Population

- We aim to recruit a convenience sample of 150 female collegiate athletes competing in sports considered high-risk for ACL tears (basketball, soccer, and volleyball)
- Participants will be from surrounding universities (Loyola Marymount, Pepperdine)
- These female collegiate athletes will be English-speaking, so there is no need for non-English speaker consent considerations. If, however, a subject wishes to discuss anything in another language, CSMC interpreter services will be requested.

3.2 Inclusion Criteria

- Female
- 18 years of age or older
- Currently playing basketball, soccer, or volleyball at Loyola Marymount or Pepperdine
- If not currently on COC, regular menstrual cycle occurring every 21-35 days

3.3 Exclusion Criteria

- Previous ACL injury (Previous ACL injury, on the same knee or the contralateral knee, places you at a significantly increased risk of subsequent ACL rupture which would provide a confounding effect in our study. Subsequent treatment of that ACL injury, whether with surgery or non-operative management, would also affect subsequent ACL injury risk.)
- Underlying neuromuscular disease
- For COC use group only: Medical contraindication to COC use
- History of pregnancy (Excluding previous pregnancies eliminates a potential confounder --- women may have lasting changes from carrying a pregnancy in the past.)
- Desire to conceive in the next year

3.4 Subject Recruitment

Female athletes will be recruited via two pathways:

(1) Approached by Dr. Trentacosta, who along with other Cedar Sinai Kerlan-Jobe doctors, serve as the team physician for the schools.
(2) Self-referral via recruitment materials posted in training facility

3.5 Subject Screening and Enrollment

All female athletes for basketball, soccer and volleyball will be provided an informational flyer about our study and be given the opportunity to approach Dr. Trentacosta via in-person meeting, telephone or email. Potential subjects who are interested will be consented for the study after discussion of the study and continued interest in participation. They will then be asked to complete a screening questionnaire evaluating medical, surgical, reproductive, and injury history. This screening questionnaire will be returned via email to the study coordinator.

Those meeting above enrollment criteria will continue participation and onboarded for the study by the study coordinator.

4.0 STUDY DESIGN AND METHODS

Data will be collected prospectively throughout participant intake and study progression.
Given the personal nature of women's contraceptive preferences, we will enroll three categories of female athletes:

(1) Women who are not on hormonal contraception and have no plan to start in the next year
(2) Women who are not on hormonal contraception and would like to initiate study COC
(3) Women who are currently on hormonal contraception and would like to switch to study COC

For those participants who would like to start study COC, women will be prescribed a daily oral contraceptive containing ethinyl estradiol 20mcg/norethindrone 1mg.

Women will maintain a contraceptive compliance diary via paper or Word document which they can submit to us in person or electronically. Orthopedic testing will start during the fourth menstrual/COC cycle due to delay in COC effect and theoretical cumulative protective effect of COC use. All three groups will undergo below testing to evaluate primary and secondary aims.

Serum Relaxin (Aim 1):

- Participants will have about 2ccs of blood drawn to measure serum relaxin levels at two time points:
    1. Baseline
    2. Fourth month of study participation - menstrual cycle-specific timing:
        - Participants not on COC:
            - Luteal phase of their menstrual cycle (Days 14-28)
            - This is when peak relaxin levels are noted to occur
        - Participants on COC
            - Pill pack days 14-28
            - Women on COC have suppressed ovulation and thus no true luteal phase, but will undergo testing during the same time period

Joint Laxity (Aim 2):

- Joint laxity will be tested at two separate time points:
    1. Baseline
    2. Fourth month of study participation – synced with serum collection for relaxin level testing.
- Joint Testing:
    - Each participant's bilateral knee joint laxity will be tested using a KT-2000 arthrometer (Medmetric Corp, San Diego, CA) for anterior and posterior laxity.
    - Laxity and biomechanical testing will be done in the athletes' training room on campus.
    - To eliminate inter-rater differences in the laxity measurement, only one examiner will conduct all knee laxity measurements.

- With a passive anterior and posterior drawer test at 67N and 87N, an average displacement (mm) for three cycles will be determined.
- A Beighton score will be calculated with goniometer by a one examiner to assess generalized hypermobility at each time point.

Motion Tracking Analysis (Aim 2):

- Participants will be kinematically evaluated using a portable, non-invasive, 3-dimensional motion capture system (Awinda, Xsens Technologies, The Netherlands).
- Each athlete will be asked to perform a singled-legged drop while the motion tracking system collects and records trunk flexion angle (degrees), hip adduction (degrees), and internal/external and coronal plane rotation (both in degrees) of the knee.
- Data will be collected and averaged over three trials at each of the two time points – baseline and 4th month of study participation.

Interval Injury Assessment (Aim 3):

- Ligamentous injury will be monitored over the entire length of the study, tracking the date, location, and mechanism of injury for each event by participant report. Follow-ups to ask about any injury will occur weekly at each training room session, or sooner if we are contacted by athlete or trainer for a more significant injury that needs to be seen urgently in the office by team physician.

Medical History Review:

- Medical history will be queried for the data points in section 5.2 at the screening visit and at Visit #1.

Schedule of Procedures

All procedures are research related

Procedures	Screening Visit	Visit #1 (4-month visit)	Phone follow-up (One year)
Medical History	X	X	
Prescribing contraception*			
Blood draw (Serum relaxin level)	X	X	
Joint Laxity Testing	X	X	
Motion Tracking analysis	X	X	
Obtain interval medical history		X	X

*Only for those who want to be put on study contraception.

5.0 DATA COLLECTION AND MANAGEMENT

5.1 Data Procurement

- Participant data will be collected by study principal investigator and co-investigators and the research coordinator.
- Participants taking study COC will keep a dairy to indicate daily adherence
    - COC diaries will be reviewed at each visit to assess patterns of day-to-day COC use.

5.2 Variables Collected

The following data points/variables will be collected:

- ID number
- Date of birth
- Medical history
- Surgical history
- Menstrual/gynecologic history
- Medications currently taking
- Social history
- Serum relaxin level
- Laxity measurements: Beighton score and anterior and posterior knee displacement (mm) during KT-2000
- Patterns of day-to-day COC use (i.e., consecutive days of OCP use reported with no more than two consecutive days of nonuse)
- Trunk flexion hip adduction, and internal/external and coronal plane rotation of the knee measured during a singled-legged drop using the motion tracking equipment mentioned above in section 4.0 (Aim 2).

5.3 Source Documents

All data for this study will be collected prospectively. Subjects' EMR or other external sources will not be accessed for use in the study.

5.4 Data Collection and Storage

Study documents will be filled out electronically the day of the visit by the investigator and/or coordinator. The documents will be labeled with a unique study ID number rather than any direct subject identifier. After signature of the study PI, data will be entered into the secure REDCap database by the research coordinator.

5.5 Confidentiality and Security of Data

Data will be coded; subject identifiers will be removed from the rest of the data and a unique study ID number assigned. The list linking identifiers to the study ID number will be kept at CSMC and will not be shared externally. This linking list will be kept in case of incidental findings. This linking document will be kept on a locked excel sheet that only the PI and research coordinator will have access to.

6.0 DATA AND SAFETY MONITORING

6.1 Data and Safety Monitoring Plan

- Only listed study staff will have access to the processed data gathered from the visits.
- Any analysis of the data will be performed on the de-identified dataset.
- As above, data from the samples will be kept and stored in the Kerlan Jobe secure network only.

6.2 Quality Control and Quality Assurance

- Dr. Trentacosta will be responsible for the evaluation, analysis, and reporting of the data among the co-investigators.

7.0 STATISTICAL CONSIDERATIONS

7.1 Study Outcome Measures

- **Data Analysis:** Statistical analysis will be performed using SAS statistical software (SAS Institute Inc., Cary, NC, USA) with significance set at $p<0.05$. Differences in the two timepoints will be evaluated between the two groups. Multiple regression will be used to analyze rate of injury as a function of OC use (group), joint laxity, motion analysis, and serum relaxion, and additional demographic data. Post-hoc ANOVA, or non-parametric alternative, will be used to evaluate continuous variables (joint laxity, motion analysis, and serum relaxin levels) between groups.
- Serum relaxin-2 level will be measured using a Quantikine Human Relaxin-2 Immunoassay (DRL200). All samples will be run in duplicate and relaxin-2 concentrations will be calculated from the standard curve. The intra-assay and inter-assay coefficients of variation and minimum detection limit will be determined and reported.
- Joint laxity measurements will be evaluated using the KT-2000 and the Beighton Score. The KT-2000 measures anterior and posterior displacement (mm) of the tibia relative to the femur when an anterior and posterior load are applied to the tibia. The amount of tibial displacement provides information on ACL laxity. The Beighton score is screening technique for measuring generalized joint hypermobility.[1] It requires the performance of 5 maneuvers, four passive bilateral and one active unilateral performance:
    1. Passive dorsiflexion and hyperextension of the fifth MCP joint beyond 90°
    2. Passive apposition of the thumb to the flexor aspect of the forearm
    3. Passive hyperextension of the elbow beyond 10°
    4. Passive hyperextension of the knee beyond 10°
    5. Active forward flexion of the trunk with the knees fully extended so that the palms of the hands rest flat on the floor

  The Beighton score is based on a 9-point scale with ≥ 4 considered hypermobile.
- Continuous measures of trunk flexion hip adduction, and internal/external and coronal plane rotation of the knee measured during a singled-legged drop using the motion tracking equipment mentioned above in section 4.0 (Aim 2). These outcomes measures are all in angles (degrees). Increased valgus knee motion (in the coronal plane) and landing with the femur in adduction and internal rotation has been suggested to predispose athletes to injury when landing from a jump.[10]

7.1 Sample Size Considerations

The primary outcome measure of this study is the rate of ligament injury. Therefore, our sample size requirements were based on this measure. Previous research indicates female athletes' risk of injury is sport dependent. In Dragoo et al.'s 2011 analysis, they report a 60% rate of ACL injury among basketball players, and a ~30% injury rate among soccer, gymnastics, and lacrosse female athletes.[4] Whereas field hockey and volleyball had a reported 0% rate of injury. Thus, we believe it is reasonable to estimate that females not taking oral contraceptives will have an estimated 30% risk of ligament injury, which we aim to demonstrate a 20% absolute reduction to 10% risk of injury among females taking OCs. Assuming equal sizing, based on previous studies that demonstrate approximately have of female athletes are on OCs,[2] we estimate a total sample size of 140 will provide approximately 80% power to detect an ACL Injury rate difference of 10% (OC) versus 30% (non-OC).

8.0 REFERENCES

1. Beighton P, Solomon L, Soskolne CL. Articular mobility in an African population. *Ann Rheum Dis.* 1973;32(5):413-418.

2. Brynhildsen J, Lennartsson H, Klemetz M, Dahlquist P, Hedin B, Hammar M. Oral contraceptive use among female elite athletes and age-matched controls and its relation to low back pain. *Acta Obstet Gynecol Scand.* 1997;76(9):873-878.

3. Chandrashekar N, Mansouri H, Slauterbeck J, Hashemi J. Sex-based differences in the tensile properties of the human anterior cruciate ligament. *J Biomech.* 2006;39(16):2943-2950.

4. Dragoo JL, Castillo TN, Braun HJ, Ridley BA, Kennedy AC, Golish SR. Prospective correlation between serum relaxin concentration and anterior cruciate ligament tears among elite collegiate female athletes. *Am J Sports Med.* 2011;39(10):2175-2180.

5. Gilmer GG, Roberts MD, Oliver GD. The Relationship between Serum Relaxin Concentrations and Knee Valgus. *Int J Sports Med.* 2020;41(3):182-188.

6. Hansen M, Kjaer M. Sex Hormones and Tendon. *Adv Exp Med Biol.* 2016;920:139-149.

7. Hashemi J, Chandrashekar N, Mansouri H, Slauterbeck JR, Hardy DM. The human anterior cruciate ligament: sex differences in ultrastructure and correlation with biomechanical properties. *J Orthop Res.* 2008;26(7):945-950.

8. Heitz NA, Eisenman PA, Beck CL, Walker JA. Hormonal changes throughout the menstrual cycle and increased anterior cruciate ligament laxity in females. *J Athl Train.* 1999;34(2):144-149.

9. Kiapour AM, Murray MM. Basic science of anterior cruciate ligament injury and repair. *Bone Joint Res.* 2014;3(2):20-31.

10. Lopes TJA, Simic M, Myer GD, Ford KR, Hewett TE, Pappas E. The Effects of Injury Prevention Programs on the Biomechanics of Landing Tasks: A Systematic Review With Meta-analysis. *Am J Sports Med.* 2018;46(6):1492-1499.

11. Rights USDoEOoC. Title IX and Sex Discrimination. Available at: https://www2.ed.gov/about/offices/list/ocr/docs/tix_dis.html.

12. Torstveit MK, Sundgot-Borgen J. Participation in leanness sports but not training volume is associated with menstrual dysfunction: a national survey of 1276 elite athletes and controls. *Br J Sports Med.* 2005;39(3):141-147.