

# Hormonal Hazards to the Knee: Comparative Analysis of Estrogen, Progestogens, and ACL Injury Risk?

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**Disclosures:** none

**INTRODUCTION:** Anterior Cruciate Ligament (ACL) injury risk is modified by contraceptive use. While it is debated on whether it is degenerative or protective, it has been postulated that the hormone relaxin may play a role in the pathophysiology. Relaxin relaxes muscles, ligaments, and joints of the body in preparation for pregnancy. It is stimulated by the peak of luteinizing hormone (LH), which occurs due to the surge in Estrogen. Estrogen and progesterone may differentially impact ACL injury risk by modulating collagen integrity and joint laxity. This study compares the impact of ACL injury risk between estrogen or progesterone.

**METHODS:** A retrospective cohort study was conducted using the TriNetX Global Collaborative Network. All sexes - females, males, and unknown- were included in this study. Two cohorts were defined: patients taking progesterone-only contraceptives (n= 1,390,653), and patients taking estrogen-only contraceptives (n= 3,426,423). Patients with prior ACL sprain or repair on or before contraceptive use were excluded. The primary outcome was incidence of ACL sprain and ACL repair. Propensity matching was used to balance the two cohorts, resulting in each cohort consisting of 1,352,150 patients each. Statistical analyses included risk analysis, Kaplan-Meier survival analysis, and frequency (number of instances) analysis. Key metrics included risk ratio, odds ratio, hazard ratio, and survival probability over a 20-year follow-up period.

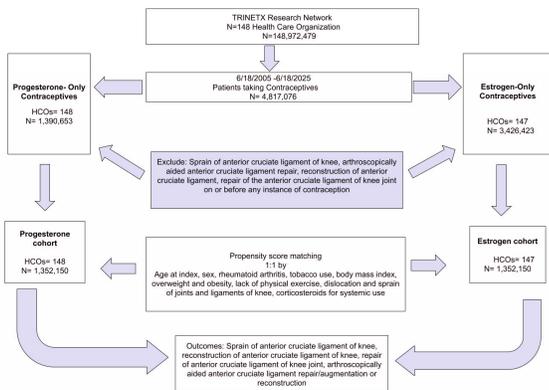
**RESULTS SECTION:** After matching, the estrogen-only contraceptives cohort was positively associated with increased risk of ACL injury (risk ratio: 0.830; 95% CI: 0.785, 0.879, favoring progesterone). Kaplan-Meier survival analysis demonstrated an increased instantaneous risk of ACL injury with estrogen (hazard ratio: 0.895; 95% CI: 0.846, 0.948; p-value < 0.001). Additionally, an increase in average subsequent injury was associated with estrogen-only contraceptive use (mean: 5.251 v. 5.810, p-value = 0.035).

**DISCUSSION:** Our findings demonstrate a significant association between estrogen-only contraceptive use and increased ACL injury risk, earlier injury onset, and higher recurrence rates compared to progesterone-only use. Estrogen's impact on ligament structure—via altered collagen synthesis and increased laxity—may underlie this heightened vulnerability<sup>1</sup>. Conversely, through the inhibition of catabolic processes as well as enhanced matrix stability, progesterone may strengthen the ligament<sup>2</sup>. These results support the hypothesis that individual hormonal components play distinct roles in ligament integrity and injury susceptibility, offering mechanistic insight that complements existing biomechanical and orthopedic literature.

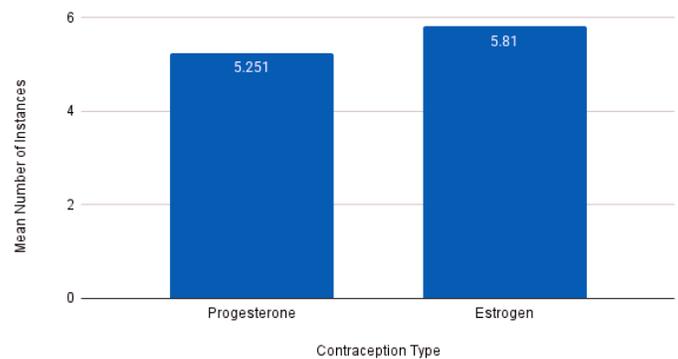
**SIGNIFICANCE/CLINICAL RELEVANCE:** (1-2 sentences): This study provides the first large-scale, head-to-head comparison of estrogen-only versus progesterone-only contraceptive use and associated ACL injury risk, revealing a significant association between estrogen exposure and increased injury and recurrence rates. These findings have clinical relevance for biomechanics, injury prevention strategies, and contraceptive counseling, highlighting estrogen modulation as a potentially modifiable risk factor in injury prevention strategies for high-risk populations.

**REFERENCES:** (1)Wood RH, Reyes R, Welsch MA, Fiala KA, Hoogstraat J, Andrews V. Concurrent oral contraceptive use enhances the detrimental effect of estradiol on exercise-induced ACL laxity. *J Orthop Res.* 2007;25(3):345-351. doi:10.1002/jor.20209. (2)Slauterbeck JR, Fuzie SF, Smith MP, et al. The menstrual cycle, sex hormones, and anterior cruciate ligament injury. *J Athl Train.* 2002;37(3):275-278.

**IMAGES AND TABLES:**



Mean Number of Instances vs. Cohort



Risk Percentage

