WebLog Journal of Orthopaedics

Research Article
Published: 12 Dec, 2025

Impact of Oral Contraceptive and Hormone Replacement Therapy Use Resulting in Increased Risk of Meniscal Degeneration in Female Athletes

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Abstract

Background: Meniscus degeneration is the gradual breakdown of cartilage in the knee that could lead to osteoarthritis. Female athletes in high-impact sports are at an increased risk, but the underlying reason for this is unknown. The deficiency of sex hormones (i.e, Estrogen) is known to influence connective tissue and joint health. Still, the impact of elevated hormones, such as those from oral contraceptives and hormone replacement therapy, is unknown. The study aims to evaluate elevated hormone levels in female athletes with the risk of meniscus injuries.

Methods: A retrospective cohort study was conducted using the TriNetX Global Collaborative Network. Two cohorts were defined: female athletes aged 15-45 on oral contraceptive or hormone replacement therapy (n=61,888), and a control group of female athletes not on hormonal therapy (n=205,175). The primary outcome was the development of meniscus injuries, including meniscus tears or meniscus derangements. Patients with meniscus-related knee injuries and osteoarthritis before hormonal therapy were excluded. Statistical analyses included risk analysis, Kaplan-Meier survival analysis, and frequency analysis (i.e., the number of instances). Key metrics included risk ratio, hazard ratio, and survival probability over a 5-year follow-up period.

Results: Oral Contraceptive Pills (OCP) and Hormone Replacement Therapy (HRT) in female athletes after matching (n=58,265, 50%) were positively associated with meniscus degeneration compared to female athletes who were not on hormone therapy (n=58,265, 50%). OCP and HRT athletes had a risk ratio of 1.369. Kaplan-Meier Analysis showed similar time-related meniscus injuries with OCP and HRT use (97.59% *vs*. 97.63%). Users demonstrated a minor increase in the average number of instances post-outcome (3.54 *vs*. 3.42). This difference was not statistically significant (p = 0.666).

Conclusions: Hormonal therapy slightly increases the number of meniscus-related injuries for female athletes. These findings suggest that oral contraception and hormone therapy may impact joint health and should be considered for future risk assessments.

Keywords: Hormone Replacement Therapy; Meniscal Degeneration; Meniscus Tear; Oral Contraceptives

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Received Date: *02 Dec 2025*
Accepted Date: *10 Dec 2025*
Published Date: *12 Dec 2025*

Citation:
Eubanks A, Allen K, Kearney D, Mills D, Ross D, Burnard M, et al. Impact of Oral Contraceptive and Hormone Replacement Therapy Use Resulting in Increased Risk of Meniscal Degeneration in Female Athletes. WebLog J Orthop. wjor.2025.l1201. https://doi.org/10.5281/zenodo.17993710

Introduction

The menisci are crescent-shaped fibrocartilaginous tissues situated between the femoral condyles and the tibial plateaus. They serve as load-bearing and stabilizing structures within the knee joint [1]. Meniscus degeneration tends to progress over time, largely because only the outer third receives sufficient blood flow, limiting its ability to be repaired. Repeated mechanical stress, including hoop and shear forces, gradually compromises the tissue's integrity [2]. This ongoing strain often culminates in complex tearing, particularly within the posterior horn and central body of the meniscus.

Structurally, the medial and the lateral meniscus are primarily comprised of fibrochondrocyte cells embedded in an extracellular matrix (ECM) [3]. Fibrochondrocytes share characteristics of both

chondrocytes, which maintain the ECM of cartilage, and fibroblasts, which regulate connective tissue structure. Fibrochondrocytes primary role is to synthesize and maintain the ECM. The ECM itself consists predominantly of water (72%) and collagen (22%), along with smaller amounts of glycoproteins, elastin, and proteoglycans [4, 5]. The meniscus is made up of two different types of collagen that help it function. Type I collagen, the main type in the meniscus, is mostly found in the outer vascular region. Type II collagen is found more in the inner avascular zone (which lacks a blood supply). The collagen is important because it provides strength and structural support and helps the tissue handle pressure and maintain flexibility. Other key components such as glycoproteins and proteoglycans make up the knee as well [4]. Understanding how these parts work together is important for identifying what may lead to knee injuries.

Exploring the factors that contribute to meniscus degeneration and other knee-related injuries is essential to understanding the risks faced by female athletes. Sports-related knee injuries are more common among female athletes than male athletes, a disparity that can be attributed to factors such as stretching routines, menstrual cycles, and physiological differences [6, 7]. Reports from the National Collegiate Athletics Association (NCAA) indicate that Women's Gymnastics, Women's Soccer, and Women's Basketball have the highest sports-related knee injury rate [8]. These sports typically involve excessive jumping, twisting, and turning, increasing the risk of anterior cruciate ligament (ACL) tears and meniscus tears. While several studies attributed the increased ACL injury risk in females to neuromuscular and anatomical differences, hormonal factors may also contribute to this disparity. Emerging evidence suggests that hormones such as estrogen and progestin may play a role in the disproportionate knee injuries observed in females.

Estrogen is a sex hormone that is important for female reproductive health. Fluctuations of estrogen (estradiol) and progesterone (progestin) drive the development of secondary sex characteristics, menstruation, and menopause later in life. During the menstrual cycle, estradiol (E2) is highest around day 14 or at the start of ovulation [9]. Peaks in progesterone (P4) occur during the luteal phase. Oral contraceptive pills inhibit ovulation by suppressing the secretion of follicle-stimulating hormone (FSH) and luteinizing hormone (LH). Importantly, understanding how these hormonal fluctuations influence musculoskeletal structures is critical, as several studies have examined the impact of the menstrual cycle on knee and ligament laxity, leading to varying results [10, 11]. These findings highlight the need for further research on how female sex hormones interact with other hormones and structures.

Understanding the structure and cellular components that make up cartilaginous tissue, such as the meniscus, is essential to understanding how estrogen may influence meniscus susceptibility to injury, particularly in female athletes. While there are studies about the influence of Estrogen on structures such as the anterior cruciate ligament, there is a lack of investigation of the hormone's effect on other cartilaginous structures, such as the meniscus. The purpose of this study is to expand on previous literature and investigate the relationship between the use of oral contraceptives and hormonal therapy on meniscus degeneration.

Methods

Study Design

This retrospective cohort study utilized data from the TriNetX Global Collaborative Network, comprising 147 healthcare organizations (HCOs) and providing access to electronic medical records from a total of 148,972,479 patients. Female athletes aged 15-45 years old were eligible for this study. Two cohorts were identified: athletes who were on oral contraceptives (OCPs) or hormonal replacement therapy (HRT) and athletes who had no hormonal therapy use. Patients with a history of knee osteoarthritis, meniscus injury, or meniscus repair procedures prior to hormonal therapy were excluded from this study.

The OCP/HRT cohort included athletes (identified using ICD-10 codes Y93, E007, Z02.5) who were either taking oral contraceptives (Medication codes: NLM:RXNORM: 4100, 14584, 6373, 22656, 11636, 6703, 6529, 6691, 7514; NLM:ATC: G03AA, G03AB, G03AC; ICD-10-CM: Z79.3) or receiving hormone replacement therapy (ICD-10-CM: Z79.890). Any patients with pre-existing osteoarthritis, meniscus tears or derangements, or meniscus repairs prior to hormonal therapy initiation were excluded. A total of 61,888 patients met the inclusion criteria for the hormonal therapy cohort.

The non-hormonal therapy cohort consisted of athletes who were not receiving oral contraceptives or hormone replacement therapy. Similar exclusion criteria were applied, removing individuals with a history of osteoarthritis, meniscal pathology, or meniscus repair prior to the index event. This cohort included a total of 205,175 patients.

The index event was defined as any meniscus related knee injury that occurred after the use of hormonal therapy. Outcomes were tracked with a 5 year follow up period starting one day after the index date. The primary outcome was meniscus injuries defined by the following ICD codes and conditions: meniscus derangements (ICD-10 codes M23.0, M23.200-209, M23.211, M23.212, M23.219, M23.300-309), meniscus tears (ICD-10 codes S83.2, S83.20, S83.24, S83.28, S83.209, S83.209A, S83.219, S83.219A, S83.242A, S83.241A, S83.241, S83.242 S83.249, S83.281, S83.281A, S83.282, S83.249A, S83.289, S83.289A, S83.28), and meniscus repairs (USMLS:SNOMED: 239419007, 84877006; UMLS:CPT: 27403, 29882).

Statistical Analysis

TriNetX's analytical tools were used for statistical analyses. To reduce confounding, a 1:1 propensity score matching was performed using the following covariates: age at index, body mass index, rheumatoid arthritis, and corticosteroid use. Matching resulted in balanced cohorts of 58,265 patients each, ensuring comparability. The OCP/HRT cohort was reduced from 61,888 to 58,265, while the non-hormonal therapy cohort was reduced from 205,175 to 58,265 patients (Figure 1). The index event was defined as the first recorded diagnosis meeting the inclusion criteria for each cohort. The analysis follows the patients for a 5-year period from the index date.

Risk calculations such as absolute risk, risk difference, and risk ratio provided an assessment of the proportion of patients diagnosed with meniscus derangements in each cohort. Survival analysis utilized Kaplan-Meier survival curves with log-rank testing and hazard ratios to estimate the time period to diagnosis. Frequency comparisons evaluated the number of degeneration related diagnoses during the study period. Statistical significance was determined at a two-sided p-value < 0.05.

Ethical Considerations

This retrospective study is exempt from informed consent. The data reviewed is a secondary analysis of existing data, does not

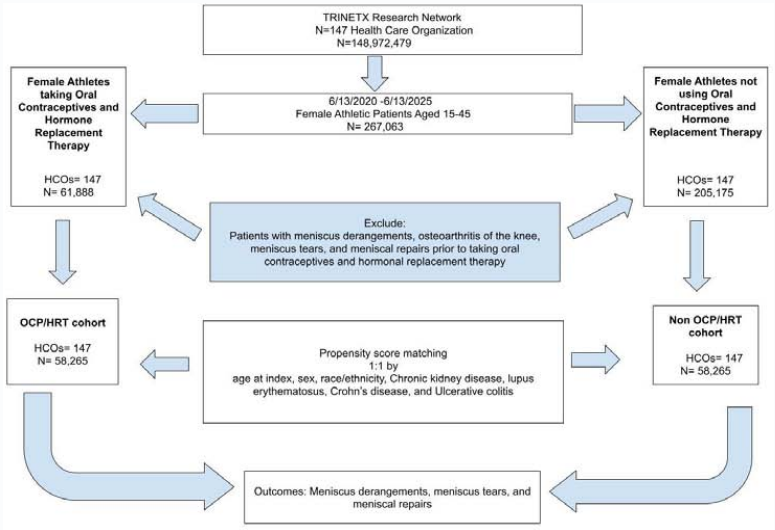

Figure 1: Flow chart of the inclusion, exclusion, and propensity matching criteria for the study. OCP/HRT (Oral contraceptives or hormonal replacement therapy).

involve intervention or interaction with human subjects, and is de-identified according to the de-identification standard defined in the HIPAA(Health Insurance Portability and Accountability Act) Privacy Rule.

Results

OCP and HRT in female athletes were associated with a slightly increased risk of developing degenerative-related conditions in the knee. In the OCP/HRT group (Cohort 1), 943 patients out of 58,265 (1.62%) after matching developed a meniscus injury or required a procedure to help correct the condition. In comparison, the non-OCP/HRT group (Cohort 2) had 689 patients of 58,265 (1.18%) who developed a degenerative condition. The risk percentage, based on the number of patients with the outcome, is visually represented in the column chart (Figure 2). This yielded a risk ratio of 1.369 (95% Cl: 1.241, 1.509) and a risk difference of 0.004 (95% Cl: 0.003, 0.006; z: 6.332; p-value: <0.001), meaning that OCP/HRT users has about a 37% greater risk of developing a meniscus injury in comparison to non-OCP/HRT users.

The survivability of not getting meniscus degeneration for patients using hormone therapy was less than athletes who were not using OCP/HRT. Cohort 1 had a 97.59% of not developing a degenerative meniscus condition at the end of 5 years versus a 97.63% survivability for athletes not taking OCPs/HRT (Figure 3). Additionally, a log-rank test indicated no statistical significance between the cohorts (x^2 =0.169, p-value= 0.681). The hazard ratio was 0.980 (p-value = 0.041), which despite reaching statistical significance, may pose a marginal reduction in the instantaneous risk among hormone users. Given the risk ratio and risk difference stated previously, the overall pattern follows a slight increased risk of meniscus injury following hormone therapy.

There was an increased mean number of athletes with a recurrence of meniscus injury after getting it the first time in the OCP/HRT cohort with 3.543 instances. Cohort 2 has a decreased mean number of instances at 3.430 athletes (Figure 4). However, the number of instances between cohorts were not statistically significant (p-value: 0.666), demonstrating a similar example of obtaining a recurring meniscus injury between both cohorts.

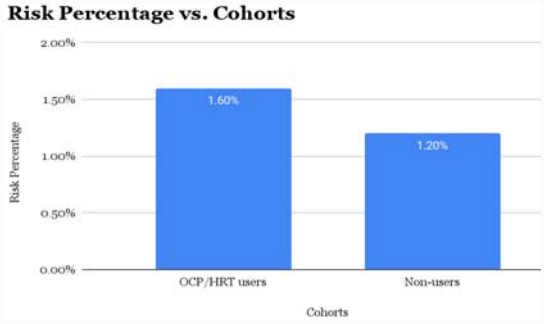

Figure 2: Column chart comparing the risk percentage or the likelihood of the expected outcome between the two cohorts - OCP/HRT users and non-users. (p-value: <0.001).

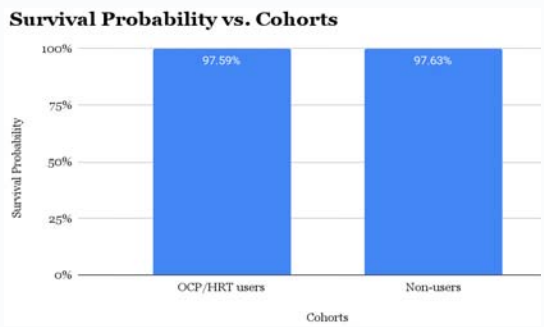

Figure 3: Column chart comparing the survival probability of the two cohorts, OCP/HRT users compared to those that do not use OCP or HRT. (p-value= 0.681).

Discussion

This study demonstrates a statistically significant association between hormonal therapy and an increased risk of meniscal injuries of the knee. Female athletes using OCPs or HRT had a 37% higher relative risk of developing a meniscus injury over a 5 year period compared to non-users. While the absolute risk difference was small (0.004), the increased risk is notably higher in female athletes taking hormonal therapy (1.6% *vs.* 1.2%). However, Kaplan-Meier survival

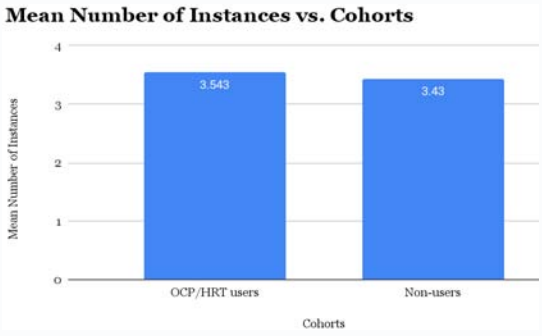

Figure 4: Column chart illustrating the mean number of instances or how many times a meniscus injury was diagnosed between OCP/HRT users and those that do not use OCP or HRT. (p-value: 0.666).

curves showed a similar injury timing between the two cohorts. The hazard ratio of 0.980 indicates that the outcome is about the same in the two groups. The average number of instances of getting another injury post-diagnosis remained similar between the two groups (~3.4), demonstrating that although there may be an increased risk of initial injury, hormonal therapy does not impact recurrent injuries.

The role of sex hormones in musculoskeletal health remains complex. While there has been evidence of increased risk for knee injury with oral contraceptives, there is also evidence suggesting a protective mechanism behind oral contraceptives and hormones on knee ligaments. DeFroda et al. observed a decrease in the amount of anterior cruciate ligament (ACL) injuries present with females aged 15-19 years [12]. Similarly, Rahr-Wagner found a decrease in the amount of operatively treated ACL injury with general use of oral contraceptives regardless of the time period of use [13]. This could likely be due to the inhibition of hormonal fluctuations in the ovarian cycle as a result of OCP use [12], which could reduce ligamentous laxity. Martineau et al. also suggests a protective mechanism of OCP's, preventing anterior knee translation in comparison with a cohort that did not use OCP's [14]. These findings conflict with other studies that have found that estrogen directly decreases collagen synthesis and tendon stiffness, likely leading to more of a risk for ACL injury [15, 16]. Another paper supports the idea that Estrogen decreases protease activity and matrix degradation in the temporomandibular joint [17]. This may not be the case for fibrocartilage in the knee, leading to an increased risk of injury instead of an expected decrease.

In contrast, other literature suggests that estrogen plays a degenerative role in fibrocartilaginous structures, such as the knee meniscus. Several studies that explored the impact of oral contraceptives and estrogen on musculoskeletal health reported an inhibitory mechanism of collagen [15] as well as a negative impact on joint health. The degeneration of the meniscus, leading to meniscus injuries could be due to the inhibition of collagen synthesis, an important structure that composes the knee meniscus [5]. Further supporting the degenerative role of oral contraceptives, studies have found an increased incidence of ACL reconstruction [18] and knee osteoarthritis [19] when examining the effects of OCP use. These findings emphasize a detrimental effect to joint health with sex hormones, not just with the lack thereof, but with its excess.

The impact of sex hormones on knee anatomy has been most recently studied in mouse models. Science has found that a decrease in hormones commonly leads to degeneration of the meniscus and osteoarthritis [20, 21], but the physiological consequence of hormonal excess is less commonly researched. While the effect of estradiol is not clear, Abate et al. reported an inhibiting mechanism of Estrogens on collagen synthesis [15], potentially increasing the risk of injury due to the weakening of structures that contain collagen. Relaxin, a hormone that peaks during the luteal phase of the ovarian system, may be the key component that is leading to an increased risk of injury. Robinson et al. postulated that this hormone may contribute to the early onset of trapeziometacarpal osteoarthritis [17] due to a decrease in the release of collagen. Notably, this peak of Relaxin, further increased with oral contraceptives [22], could likely be the mechanism behind an increase in meniscal injuries of the knee, further leading to the development of knee osteoarthritis. Hashem et al. found that relaxin can induce degeneration of fibrocartilage, which was modulated by estrogen and attenuated with progesterone [23]. Paradoxically, Robinson et al. have found that estradiols promote chondrogenesis via ERα receptors that are present in the temporomandibular joint [24], highlighting the complex relationship of hormones on joint health. These studies only emphasize the need for targeted investigation of sex hormones and its impact on the body to consider possible consequences in populations using OCP's and HRT.

Our study builds on this growing research, providing a thorough inclusion and exclusion criteria from a worldwide database to form concise cohorts. By using an at-risk group (female athletes), including various brands and forms of oral contraceptives, and excluding athletes who had prior conditions that could affect meniscus health, this study provides a more precise understanding of how hormonal therapy affects living patients. Propensity matching proved to be significant as rheumatoid arthritis, and corticosteroid use impacts joint health and would have been confounding variables with the results. While studies that suggest degenerative mechanisms of estrogen and sex hormones utilize mouse models, this study uses real world data from real patients to find a conclusion. Our study mostly supports the experiment done by Hashem et al., exploring the effects of different sex hormones and their combinations. It was found that Relaxin and Beta Estradiol had a significant impact on synovial joints, except the knee meniscus [24]. With our findings, it was found that there was a statistically significant increased risk for the development of meniscus injury with OCP and HRT use. Previous studies may argue that there could be a protective mechanism of oral contraceptives and hormonal therapy because of the lack of variation in hormones, providing stability, but our data opposes this idea, showing an increased risk of meniscus injuries, likely due to an excess in hormones.

Future research should aim to include groups such as transgender, intersex, and male patients undergoing hormonal therapy. By including these groups, considering the difference in the biomechanics of hormonal therapy, it could provide a greater understanding of sex hormones and its impact on joint health. Dosage, duration, and type of hormonal therapy should also be considered in future studies, as the amount and length of time taking synthetic hormones could have a detrimental effect on some areas of the musculoskeletal system. Future studies should also investigate whether taking OCP's and undergoing HRT during reproductive years proves to have an increased risk in chronic and degenerative diagnoses when patients reach menopause. Tracking the long term effects of hormonal therapy would provide an understanding of the cumulative effects of such drugs.

Limitations

Although propensity score matching was utilized, the potential for residual confounding cannot be excluded. Variability in diagnostic accuracy over the 5 year study period, along with advancements in healthcare practices and follow-up protocols, may have affected the validity of the findings.

Conclusion

This 5 year study dives into the complex relationships of sex hormones and its impact of the knee meniscus. Female athletes aged 15-45 years were divided into two cohorts - patients taking Oral Contraceptives and Hormonal therapy and patients that were not. Individuals were excluded if they experienced a meniscus injury, osteoarthritis of the knee, or meniscus repair prior to taking hormonal therapy. Confounding factors such as age, BMI, Rheumatoid arthritis, and corticosteroid use were matched to balance each cohort. The results showed a 37% increased risk for getting a meniscus injury with hormonal therapy, compared to those not taking hormonal therapy. There was no significant time to event difference or increased incidence of subsequent injury. These findings go against previous studies, signifying a degenerative mechanism behind an excess of sex hormones in females. Future studies should investigate the effects of synthetic sex hormones on additional populations, such as transgender individuals and reproductive-aged females, to further understand the effect of hormones on musculoskeletal health.

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