# The Effect of Menstrual Cycle and Contraceptives on ACL Injuries and Laxity

## A Systematic Review and Meta-analysis

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**Background:** Women are at substantially greater risk for anterior cruciate ligament (ACL) injuries than are men.

**Purpose:** To conduct a systematic review and meta-analysis of the literature to clarify the effect of the menstrual cycle and contraceptives on the laxity of and noncontact injuries to the ACL.

**Study Design:** Systematic review; Level of evidence, 4.

**Methods:** Searches were conducted using MEDLINE (1946–August 2016), the Cochrane Library Database, clinical trial registries, and related reference lists. Search terms included *athletic injuries*, *knee injuries*, *ligaments*, *joint instability*, *menstrual cycle*, *ovulation*, *hormones*, and *contraceptives*. Investigators independently dually abstracted and reviewed study details and quality using predefined criteria and evaluated overall strength of evidence using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) criteria.

**Results:** Twenty-one studies totaling 68,758 participants were included: 5 on the menstrual cycle and ACL injury, 7 on hormonal contraceptives and ACL injury, as well as 13 on menstrual cycle and ligament laxity. Four of 5 studies of women not using hormonal contraception indicated that the luteal phase was the least associated with ACL injuries. The 2 largest and highest quality studies on hormonal contraceptives suggested that hormonal contraceptives may be protective against ACL injury. Six of 12 studies on ACL laxity provided quantitative data for meta-analysis, finding significantly increased laxity during the ovulatory phase compared with the follicular phase.

**Conclusion:** The literature suggests an association between hormonal fluctuations and ACL injury. Recent studies have suggested that oral contraceptives may offer up to a 20% reduction in risk of injury. The literature on ACL injuries and the menstrual cycle has more than doubled over the past decade, permitting quantitative analysis for the first time. However, the overall strength of this evidence is low. Promising potential directions for future research include long-term observational studies with ongoing hormonal assays and large interventional trials of follicular suppression, including newer hormonal methods.

**Keywords:** anterior cruciate ligament; knee injury; hormonal contraceptives; female; human; menstrual cycle; systematic review; meta-analysis; sports medicine

As participation in sports has become increasingly popular among American youth, so too have anterior cruciate ligament (ACL) injuries, increasing 2.3% per year for children between the ages of 6 and 18 years in the United States.[4] Overall, ACL injuries have steadily increased over the past 20 years, with a current annual incidence of 200,000.[37] The short- and long-term consequences of ACL injuries—including reconstructive surgery, long-term rehabilitation, and premature osteoarthritis[51]—are costly, with an estimated financial burden of $7.6 billion per year when treated with surgical reconstruction and $17.7 billion per year when treated with rehabilitation in the United States.[37]

ACL injuries can be especially devastating and even career ending for athletes, with the rate of return to sports being less than 50%.[8] Given the ramifications of ACL injuries to society, prevention is critical.

Women and girls are at particularly high risk for ACL injuries, with rates 3 to 6 times greater than men, leading some to suggest a hormonal effect.[25] Estradiol, progesterone, and relaxin are the predominant hormones that have been studied in the menstrual cycle relating to ACL laxity. Estradiol and progesterone are at their lowest levels during menses at the beginning of the menstrual cycle (days 1-6). Estradiol reaches its peak concentration around the time of ovulation (days 12-14), with a second lower rise in the luteal phase (days 20-24). Progesterone begins a gradual rise in the late follicular phase just before ovulation, but its highest levels are reached in the mid-luteal phase (days 19-24).

These periodic hormonal fluctuations in the menstrual cycle have been postulated to cause ligament laxity, increasing the risk for ACL injuries. Specifically, laboratory studies have found that exposure of the ACL to estradiol results in a dose-dependent reduction in fibroblast and collagen synthesis and that this effect is attenuated by the addition of progestins.[56,57] Relaxin is a hormone produced by the ovary and placenta that contributes to laxity of the pubic symphysis in pregnancy and childbirth and has similarly been postulated to have an effect on the ACL in nonpregnant women.[18] A small prospective study of elite female athletes playing National Collegiate Athletic Association (NCAA) Division 1 sports found that athletes with relaxin levels greater than 6.0 pg/mL were 4 times more likely to sustain an ACL tear.[15]

This systematic review examined the effect of the menstrual cycle and hormonal contraceptives on noncontact ACL injuries and laxity.

## METHODS

The protocol for this meta-analysis is registered with PROSPERO (CRD42016032794. Found at: https://www.crd.york.ac.uk/PROSPERO/). We conducted this review following Institute of Medicine, Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), and Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidance for systematic reviews and meta-analyses.[38,39,50]

### Data Sources and Searches

A research librarian, experienced in conducting systematic reviews, searched Ovid MEDLINE (1946 to July 29, 2016) and the Cochrane Library Database. Investigators (S.D.H., M.L.M., J-M.G.) supplemented electronic searches with hand-searching of reference lists of retrieved articles. Searches were peer reviewed by a second research librarian, as suggested by the Institute of Medicine, using the Peer Review of Electronic Search Strategies (PRESS) tool.[43] The search included MeSH (Medical Subject Headings) terms and key words relating to athletic injuries, knee injuries, ligaments, joint instability, menstrual cycle, ovulation, hormones, and contraceptives.

### Study Selection

Two independent reviewers (S.D.H., M.L.M.) identified relevant studies. Included in the review were randomized trials, cohort studies, case-control studies, and case series studies with more than 10 participants that evaluated the association between either menstrual cycle or hormonal contraceptives on either noncontact injury or laxity of the ACL. Discrepancies were resolved through discussion by the review team (S.D.H., M.L.M., J-M.G., W.L., J.B.).

Studies were excluded if they were published exclusively as abstracts, had sample sizes less than 10, included pregnant women, or did not report results specific to phases of the menstrual cycle. Figure 1 provides details on the included and excluded studies at both the abstract and full-text levels.

### Data Extraction and Risk of Bias Assessment

Two independent reviewers extracted data, including study details, population, setting, results, potential confounders, follow-up, and analytic approach. Discrepancies were reconciled through discussion. The risk of bias (labeled as *good*, *fair*, or *poor* study quality) was assessed independently by 2 reviewers for each study using the United States Preventive Services Task Force (USPSTF) criteria.[21] Discrepancies were resolved through discussion by the review team (S.D.H., M.L.M., J-M.G., W.L., J.B.). A "best evidence" approach was applied, in which studies with the highest quality and most rigorous design were emphasized.

### Data Synthesis

Meta-analysis is useful to obtain precise summary estimates for outcomes. To determine the appropriateness of meta-analysis, we considered clinical and methodological diversity and assessed statistical heterogeneity. Only the outcome of knee laxity was eligible for meta-analysis. Means and standard deviations of knee laxity in each phase of the menstrual cycle were abstracted from included studies. In the KT-1000/2000 tests (MEDmetric Corp), knee laxity is commonly measured at 2 force levels: 134 and 89 N.[13] If results from both levels were reported, we used the average in the primary analysis and separate levels in the sensitivity analysis. The pairwise mean differences among the menstrual cycle phases were calculated and combined across studies. The calculation of standard error for the mean difference assumed the correlation between menstrual phases to be 0.50. Additional sensitivity analyses were conducted assuming alternative values of the correlation (0.3 and 0.8).

The DerSimonian-Laird random-effects model was used to combine studies, given the minimally detectable between study heterogeneity.[31] The calculation of 95% CI for the combined estimates was adjusted for the multiple comparisons across menstrual phases (ovulatory vs follicular, luteal vs ovulatory, and luteal vs follicular) using Bonferroni correction. Statistical heterogeneity among the studies was

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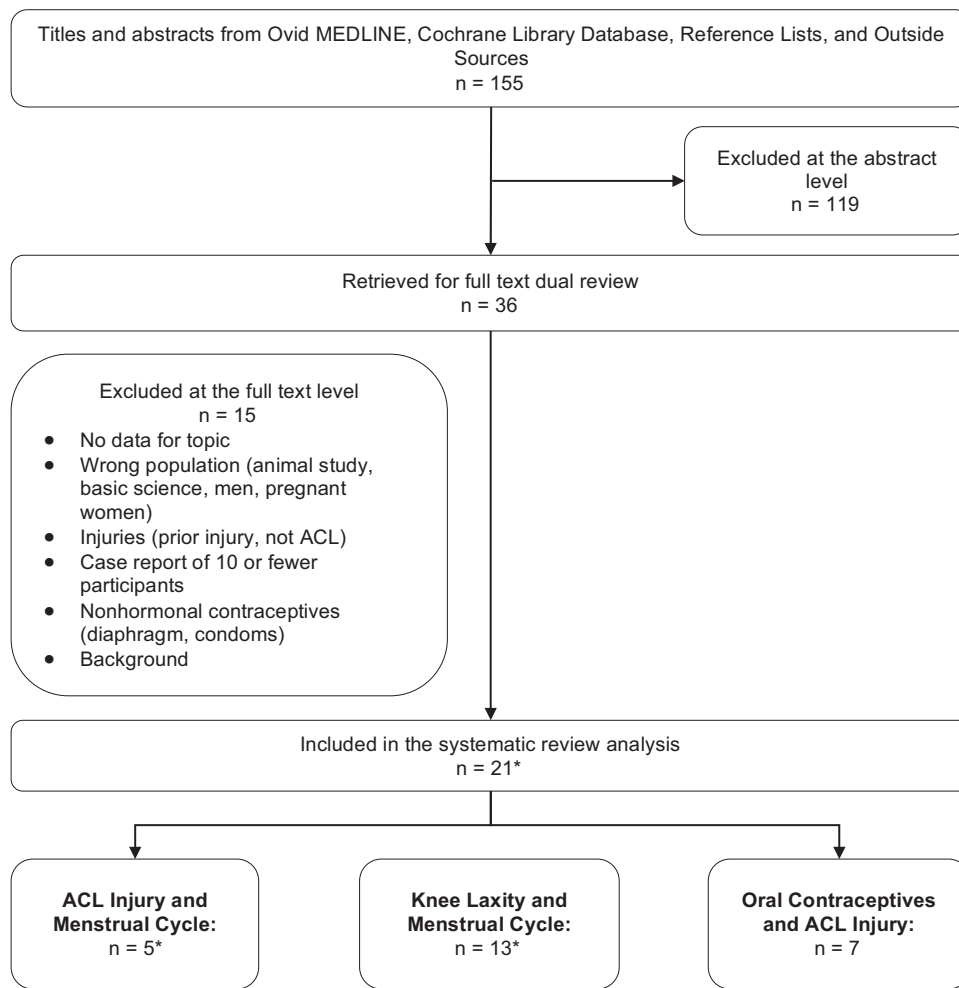
**Figure 1.** Literature flowchart. Background refers to articles that did not provide data but were helpful as background reading for the topic. *Studies overlap.

assessed using the standard Cochran chi-square test, and the magnitude of heterogeneity by using the $I^2$ statistic.[27] Results from the sensitivity analyses were similar and are not separately reported. All analyses were performed using Stata/IC 13.1 (StataCorp).

### Overall Assessment of the Strength of Evidence

The quality of evidence for each finding was rated based on criteria established by the GRADE (Grading of Recommendations Assessment, Development and Evaluation) Working Group (GRADEWorkingGroup.org). The overall judgment of the strength of evidence was classified as *high*, *moderate*, *low*, or *very low* based on study design, magnitude of the association, and consistency of the results across studies.

### RESULTS

Of the 155 potentially relevant titles and abstracts, 36 met eligibility criteria for full-text review. A total of 21 articles

met our inclusion criteria and were included in the final synthesis: 5 met inclusion the menstrual cycle and ACL injury, 7 for hormonal contraceptives and ACL injury, and 13 for ACL laxity and the menstrual cycle. Three studies overlapped across 2 categories, and 2 studies were published in multiple articles. The search and selection of studies are summarized in Figure 1.

### ACL Injury and the Menstrual Cycle

Five studies, 4 poor-quality and 1 fair-quality, examined the incidence of ACL injury and the menstrual cycle: 2 case-control studies[7,44] and 3 case series[1,3,54] (Table 1). Two studies separated the menstrual cycle into 2 phases, preovulatory and postovulatory.[7,44] Both found the incidence of ACL injury was highest in the preovulatory phase. Three studies divided the menstrual cycle into 3 phases: follicular, ovulatory, and luteal. Two of those studies found the incidence of ACL injury was highest in the ovulatory phase,[1,54] and 1 study found the highest incidence in the follicular phase.[3] Figure 2 presents a schematic of the fluctuations in estradiol and progesterone

TABLE 1
ACL Injury and the Menstrual Cycle[a]

| First Author, Date, Study Design (Quality) | Population (Sample Size, n) | Methods of Determining ACL Injury and Menstrual Cycle | Injury | | | Findings |
|---|---|---|---|---|---|---|
| | | | Follicular | Ovulatory | Luteal | |
| Beynnon,[7] 2006, case-control (fair) | Cases (n = 46): skiers with ACL injuries Controls (n = 45): uninjured alpine skier, not a relative/ friend of the injured skier | Questionnaire and serum samples | Based on history: 57% Based on progesterone levels: 73.9% | | Based on history: 43% Based on progesterone level: 26.1% | Increased likelihood of ACL injury in preovulatory phase |
| Ruedl,[44] 2009, case-control (poor) | Cases (n = 93): injured alpine skiers from a nearby clinic Controls (n = 93): uninjured skiers randomly selected from the lodge | MRI and questionnaire | Patients: 35 (57.4%) Controls: 25 (41.7%) | | Patients: 26 (42.6%) Controls: 35 (58.3%) | Increased likelihood of ACL injury in preovulatory phase |
| Wojtys,[54] 2002, case series, (poor) | Cases (n = 65): women with acute ACL injuries from local high schools, college, and 4 surrounding test sites | Questionnaire and urine assays | 13/51 (25%) | 24/51 (47%) | 14/51 (27%) | Increased likelihood for ACL injury in ovulatory phase |
| Adachi,[1] 2008, case series (poor) | Cases (n = 18): teenagers with noncontact ACL injuries | MRI and questionnaire | 2/18 (11%) | 13/18 (72%) | 3/17 (17%) | Increased likelihood for ACL injury in the ovulatory phase |
| Arendt,[3] 2002, case series (poor) | Cases (n = 83): athletes with noncontact ACL injuries from 1996 to 1998 | Reported by athletic trainer at the school | 26/58 (44.8%) | 10/58 (17.2%) | 22/58 (37.9%) | Increased likelihood for ACL injury in the follicular phase |

[a]ACL, anterior cruciate ligament; MRI, magnetic resonance imaging.

levels and the classification of menstrual phase used in each of the 5 studies.[49] Taken together, these studies suggest that the lowest risk time in the menstrual cycle for ACL injuries is in the luteal phase.

## Hormonal Contraceptives and ACL Injury

As Table 2 shows, 7 studies investigated the effects of hormonal contraception on ACL injury. There were 4 studies conducted in the United States (US),[20,22,23,26] 1 in Austria,[44] 1 in France,[33] and 1 in Denmark.[42] The studies ranged in size from 65 to 51,348 participants. Because the question of relative reduction in injury by hormonal contraceptive use requires a joint distribution of ACL injuries and contraceptive users, the most reliable estimates came from the 2 largest and highest quality studies[20,42]; both suggested a nearly 20% reduced risk for ACL injury while on oral contraceptives (OCs).

The first was a population-based case-control study from Denmark,[42] where all citizens are registered in medical and administrative databases and are given a unique ID number that allows linkage across these databases. The investigators obtained information about ACL injuries through the Danish Knee Ligament Reconstruction Register and Danish National Registry of Patients and obtained information about exposure to OC from the Danish Prescription Registry. This study identified 4497 women with an ACL injury requiring surgery and 8858 age-matched controls with no ACL injury and found an 18% reduction in risk of ACL injury

requiring surgery among OC users (relative risk [RR], 0.82; 95% CI, 0.75-0.90). The second was a US population–based case-control study using a large commercial insurance database (Clinformatics Data Mart).[20] This study identified 12,819 cases of women sustaining ACL injuries requiring surgery and a randomly selected sample of 38,457 age-matched controls. Similar to findings in the Denmark study, the US analysis found a nearly 20% reduction in risk for OC users (adjusted odds ratio, 0.82; 95% CI, 0.75-0.91).

## Knee Laxity and the Menstrual Cycle

Twelve studies examined knee laxity across the menstrual cycle.[††] Of these, 4 fair-quality[9,24,26,40] and 2 poor-quality[5,14] studies provided quantitative data for the meta-analysis; the remaining 6 studies[6,28,30,32,47,48] with fair-quality cohort study findings are reported in Table 3.

Results and 95% CIs for the 6 studies[5,9,14,24,26,40] with data suitable for meta-analysis are presented in Figure 3. Looking across studies and menstrual phases, knee laxity was significantly increased in the ovulatory phase compared with the follicular phase (mean difference, 0.36 mm; 95% CI, 0.08-0.65). Knee laxity did not differ between luteal and ovulatory phases or between luteal and follicular phases. It is unclear whether these measured differences are clinically significant. Of the remaining 6 fair-quality studies that did not report quantitative summary measures appropriate for

[††]References 5, 6, 9, 14, 24, 26, 28, 30, 32, 40, 47, 48.
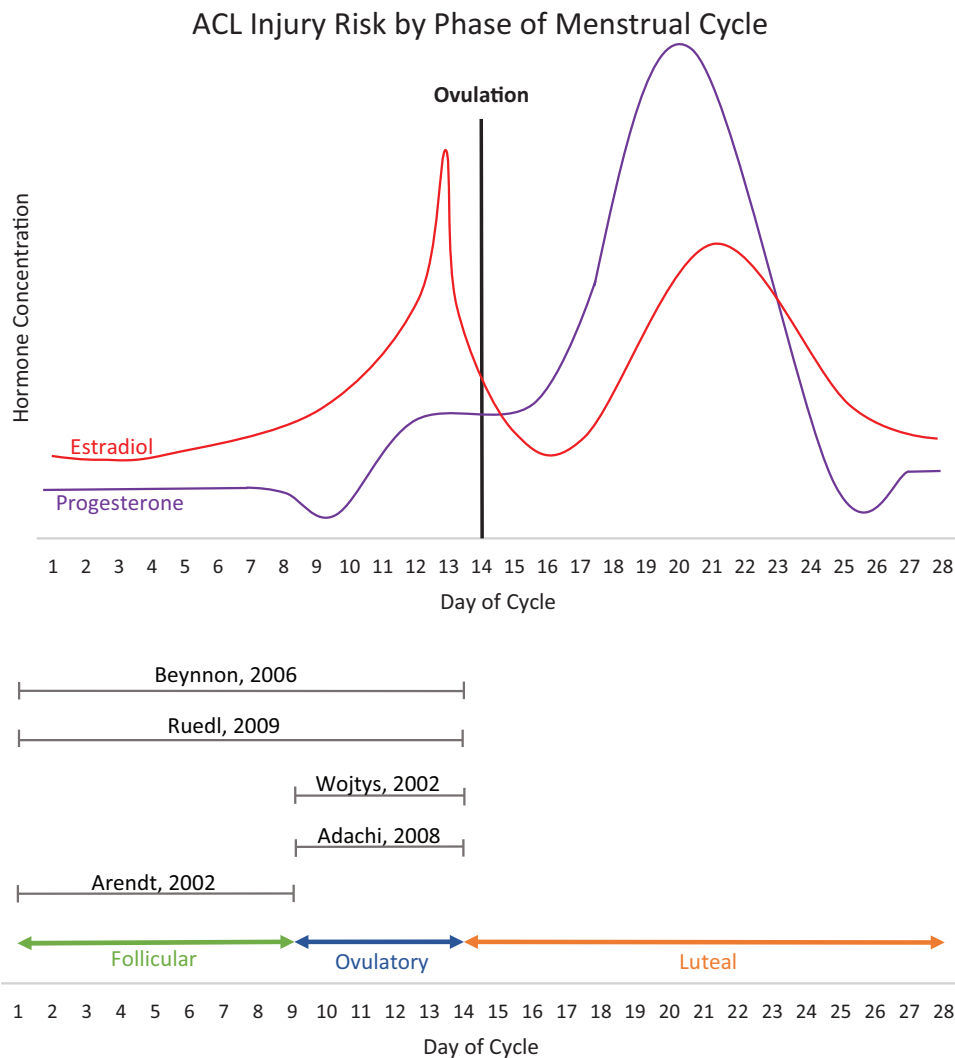
**Figure 2.** Fluctuations in estradiol and progesterone Levels. *Adapted from Speroff and Fritz.[49]

inclusion in the meta-analysis, 3 reports similarly found increased laxity in the ovulatory phase,[30,32,47] 1 found the highest laxity in the luteal phase,[48] and 2 reported no variation in laxity across the menstrual cycle.[6,28]

These same 12 studies[††] related ACL laxity to estradiol levels. Because self-reported cycle length is notoriously inaccurate, we focused on the 5 fair-quality studies[6,28,30,32,47] that provided quantitative data for both estradiol concentration and ACL laxity. To understand whether the estradiol peak or rapid decline affects laxity, measurements across studies at select times were examined: day 1 (menses; lowest estradiol concentration), days 8 to 10 (follicular), days 13-15 (ovulation), and day 22 (luteal) among these 5 studies (Table 4). Four of the 5 studies[28,30,32,47] reported highest ligament laxity when estradiol concentration was highest, suggesting that estradiol may be contributing to increased laxity. While 3 studies[30,32,47] reported the highest estradiol concentration in the follicular phase as expected, 1 study[28] reported the highest peak at day 22 (late luteal phase). Although there was a second estradiol peak in

the luteal phase, the highest occured in the follicular phase. Finally, it was unclear why the ACL laxity measurements in 1 study[6] were nearly double that of the others and why estradiol levels in 1 study[28] were lower than physiological levels.

### Overall Strength of Evidence

Following the GRADE approach, the evidence for this review was classified as "very low" in that "We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect" (GRADEWorkingGroup.org).

### DISCUSSION

Studies to date suggest that knee ligament laxity and risk of ACL injury may be increased during the ovulatory phase of the menstrual cycle and that suppression of

TABLE 2
Hormonal Contraceptives and ACL Injury[a]

| First Author, Date, Study Design (Quality) | Population (Sample Size, n) | Methods of Determining Cycle Phase and OC Use | On Hormonal Contraception | Off Hormonal Contraception | Findings |
|---|---|---|---|---|---|
| Agel,[2] 2006, cohort (poor) | NCAA women's soccer and basketball players (n = 3150) | Reported by athletic trainers to centralized injury surveillance system | Injury: 16/1124 (1.42%) | Injury: 29/2026 (1.43%) | Hormonal contraceptive use had no effect on ACL injury |
| Rahr-Wagner,[42] 2014, case-control (good) | Women with operatively treated ACL injury registered in the Danish Knee Ligament Reconstruction Registry (n = 4497 cases; 8858 controls) | Danish Knee Ligament Reconstruction Registry linked to Danish Prescription Registry records for 5 years preceding date of injury | Cases: 2047/4497 (45.5%) Controls: 4218/8858 (47.6%) | Cases: 2450/4497 (54.5%) Controls: 4640/8858 (52.4%) | OC use decreased risk of operatively treated ACL injury for long term RR 0.80 (95% CI, 0.74-0.91) and recent OC users RR 0.81 (95% CI, 0.72-0.89) |
| Ruedl,[44] 2009, case-control (poor) | Female recreational alpine skiers (n = 93 cases; 93 controls) | MRI confirmed ACL, with questionnaire for OC use and cycle phase | Cases: 32/93 (34.4%) Controls: 33/93 (35.5%) | Cases: 61/93 (65.6%) Controls: 60/93 (64.5%) | OC use had no effect (0.95, 95% CI, 0.52-1.74) |
| Wojtys,[54] 2002, case series (poor) | High school or college-aged women with ACL injuries (n = 65) | Urine assays and questionnaire | 14/65 (21.5%) | 51/65 (78.5%) | Women not taking OCs sustained more injuries during the ovulatory phase ($\chi^2 = 29.8$; $P < .0001$). Women taking OCs demonstrated no change in risk ($\chi^2 = 2.38$; $P = .7$) |
| Lefevre,[33] 2013, case series (poor) | Female skiers with ACL injuries (n = 172) | Questionnaire | 53/172 (30.8%) | 119/172 (69.2%) | OC use had no effect on ACL injury rates (85/119 [71.4%] OC vs 36/53 no OC, OR, 1.18; 95% CI, 0.59-2.38; $P = 0.64$]) |
| Arendt,[3] 2002, cohort (poor) | Female collegiate athletes (n = 83) | Reported by athletic trainers to centralized surveillance system | 20/25 (80%) | 54/58 (93%) | OC users had a greater difference between high- and low-risk periods of ACL injury, but OC use did not change the period of high risk (follicular) |
| Gray,[20] 2015, case-control (fair) | Females with ACL injury, aged 15-39 years (n = 12,891 cases; 38,457 controls) | ICD-9-CM procedural codes applied to a national insurance claim database | Cases: <90 d of use: 598/12,891 (4.6%) >90 d of use: 2408/12,891 (4.7%) Controls: <90 d of use: 1911/38,457 (5.0%) >90 d of use: 6864/38,457 (17.8%) | Cases: 9885/12,891 (76.7%) Controls: 29,682/38,457 (77.2%) | OC use decreased risk of ACL reconstructions in women 15-19 y (adjusted OR, 0.82; 95% CI, 0.75-0.91; $P = .0001$) OC use higher in older age groups 25-29 and 30-34 y (adjusted OR, 1.15; 95% CI, 1.02-1.30; $P < 0.05$ and 1.16; 95% CI, 1.04-1.31; $P < .05$) |

[a]ACL, anterior cruciate ligament; ICD-9-CM, International Classification of Diseases Ninth Revision Clinical Modification; MRI, magnetic resonance imaging; NCAA, National Collegiate Athletic Association; OC, oral contraceptive; OR, odds ratio; RR, relative risk.

TABLE 3
Knee Laxity and the Menstrual Cycle[a]

| First Author, Date, Study Design (Quality) | Sample Size, n | Methods of Determining ACL Laxity and Menstrual Phase | Data | Findings |
|---|---|---|---|---|
| Beynnon,[6] 2005, cohort (fair) | 17 | KT-1000 and Ovuquick | Early follicular: 3.1 mm (0.98)<br>Late follicular: 3.1 mm (0.95)<br>Mid-luteal: 3.2 mm (0.86)<br>Late luteal: 3.3 mm (1.27) | No change in laxity across cycle |
| Hoffman,[28] 2008, cohort, (fair) | 28 | KT-2000 with compu-KT and self-report of phase in cycle with saliva measurements of hormones | Unable to determine summary measures of laxity, and statistical contrast | No change in laxity across cycle |
| Khowailed,[30] 2015, cohort (fair) | 12 | KT-2000 and blood assays | Early follicular: 4.18 mm (0.27)<br>Ovulatory: 5.75 mm (0.47)<br>($P < .001$) | Increased laxity in the ovulatory phase |
| Lee,[32] 2013, cohort (fair) | 19 | KT-2000 and self-report | Menses: 5.1 mm (1.5)<br>Follicular: 5.4 mm (1.7)<br>Ovulatory: 5.9 mm (1.7)<br>Luteal: 5.7 mm (1.7)<br>($P < .01$) | Increased laxity in the ovulatory and luteal phases |
| Shultz,[47] 2005, cohort (fair) | 22 | KT-2000 and CVS One-Step Ovulation Predictor | Unable to determine summary measures of laxity and statistical contrast | Inconsistent findings of increased laxity in late follicular phase near ovulation and early luteal, relative to menses (significant) |
| Shultz,[48] 2010, cohort (fair) | 74 | KT-2000 and CVS One-Step Ovulation Predictor | 14-16 visits but only tested twice<br>T1 (menses): 6.7 mm (1.9)<br>T2 (early luteal phase): 7.4 mm (2.1)<br>($P < .001$) | Increased laxity in the early luteal phase |

[a]ACL, anterior cruciate ligament.

follicular development and ovulation with hormonal contraceptives may reduce this risk. This finding differs from the last systematic review on this subject, published almost a decade ago.[25] Since that time, the number of published studies has more than doubled and the total number of included participants increased from 382 to 68,758. Thus, one of the strengths of this review is a much larger body of evidence, allowing the use of quantitative meta-analysis to provide summary measures. Although the literature has increased substantially, the overall strength of this evidence, and therefore confidence in the findings, remains low.

Studies to date suggest a potential connection between hormonal levels in the menstrual cycle and knee laxity and/or injury. Several theories exist regarding the higher incidence of ACL rupture in women versus men, including anatomic differences,[‡‡] dynamic factors such as jumping and landing mechanics,[11,19,36,58] and ligamentous laxity. Fluctuations in hormones have been hypothesized to potentially play a role in the latter two. Hormones have been hypothesized to influence ACL injury by exerting a direct effect of ligament laxity or stiffness through collagen synthesis and tensile properties given estrogen, progesterone, testosterone, and relaxin receptors on the ACL or through

neuromuscular changes affecting knee alignment.[16,35,45] ACLs exposed to increased estradiol in cell culture show decreased fibroblast proliferation and alterations in collagen synthesis, whereas progesterone is associated with increased fibroblast proliferation and increased collagen synthesis.[56,57]

Hormones have also been hypothesized to exert an effect through neuromuscular changes that are thought to affect knee alignment. Two included studies[24,30] looked at the effect of hormonal fluctuations on neuromuscular activity. Both used electromyography (EMG) to measure the neuromuscular activity of the quadriceps and hamstrings. One study found no difference,[24] while the other[30] found increased activity in the follicular phase, with most pronounced effect in the lateral quadriceps (as measured by EMG activity) whereas hamstring activity was increased in the ovulatory compared with the follicular phase. Specifically, the medial hamstring had the greatest activity before impact.[30] Khowailed et al[30] suggested that these differences result in misalignment of the knee prior to impact and may contribute to increased ACL injuries observed in the ovulatory period.

Several authors[§§] have investigated the possibility of the hormonal variations in the menstrual cycle playing a role in

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‡‡References 10, 12, 17, 22, 23, 29, 34, 46, 52, 53, 55.

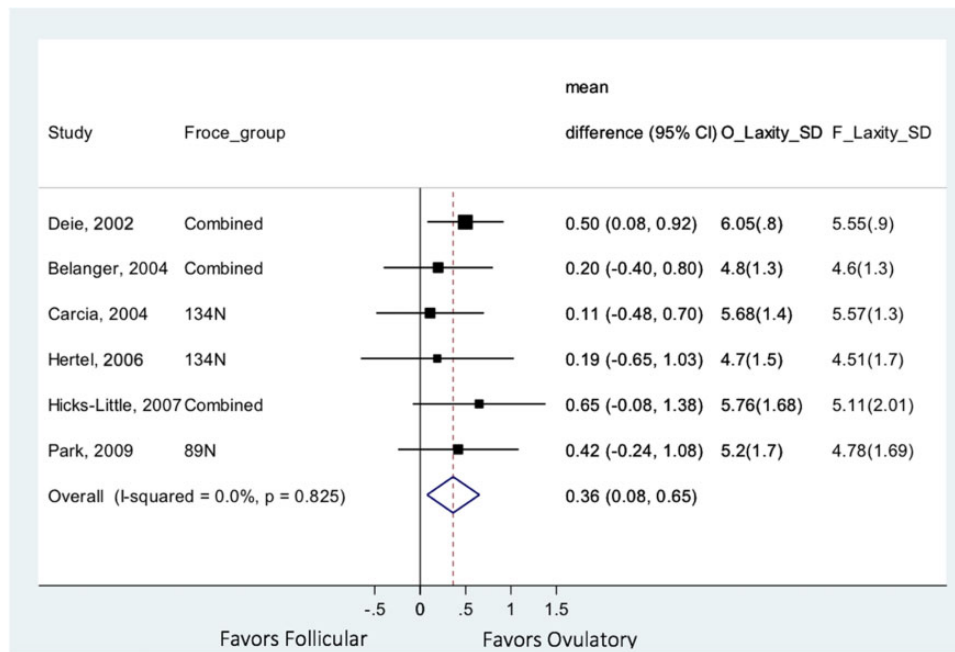§§References 10, 12, 16, 17, 22, 23, 29, 34, 35, 45 46, 52, 53, 55.

**Figure 3.** Meta-analysis: knee laxity in follicular versus ovulatory phases.

TABLE 4
Estradiol Levels and Laxity Measurements

| First Author, Date | | Menses, d | | | | Testing Methods |
|---|---|---|---|---|---|---|
| | | 1 | 8-10 | 13-15 | 22 | |
| Khowailed,[30] 2015 | Estradiol, pg/mL | 34 | — | 207.74 | — | ClearBlue ovulatory test; KT-2000 |
| | Laxity, mm | 4.18 | — | 5.74 | — | |
| Hoffman,[28] 2008 | Estradiol, pg/mL | 1.52 | 2.23-2.41 | 2.31 | 3.6 | Self-report; KT-2000 |
| | Laxity, mm | 5.29 | 5.16-5.25 | 5.44 | 5.72 | |
| Shultz,[47] 2005 | Estradiol, pg/mL | 50 | — | 175 | 129-138 | Ovulatory test; KT-2000 |
| | Laxity, mm | 5.0 | — | 5.4 | 5.4-5.3 | |
| Beynnon,[6] 2005 | Estradiol, pg/mL | 50 | — | 200 | 175 | Ovuquick; bloodwork; KT-1000 |
| | Laxity, mm | 9.1 | — | 8.9 (11.13) | 8.7 | |
| Lee,[32] 2013 | Estradiol, pg/mL | 51.4 | 82.5 | 175 | 130 | Ovulatory test; KT-2000 |
| | Laxity, mm | 5.1 | 5.4 | 5.9 | 5.7 | |

joint laxity and possibly predisposition to instability and resultant ligament rupture. The higher rate of noncontact ACL ruptures in women has raised particular interest in ligamentous laxity as a potential contributor. The classic noncontact ACL injury mechanism involves a combination of change of direction, internal rotation, and valgus across the knee. The tibia internally rotates and translates anteriorly, creating a "pivot shift" and placing the ACL in excessive tension. Any increase in ligamentous laxity, therefore, might allow more tibiofemoral motion and increase the risk of injury.

If the hormonal fluctuations involved in ovulation cause an increase in ACL rupture risk, suppression of follicular development and ovulation could be protective. While smaller studies found no effect, larger studies[20,42] powered to detect a difference in the joint association between hormonal contraception and ACL injury suggested a potential 20% reduction in risk. It is possible that the relative progesterone dominance of hormonal contraceptives mitigates the effect of estradiol. However, the 2 studies that suggested this association[20,42] were based on administrative data from patients undergoing surgery. While the studies attempted to adjust for important confounders such as age, it is impossible to assign cause and effect due to the retrospective nature of these studies. These interesting findings, however, suggest that a large long-term cohort study of female elite athletes on and off OCs or an interventional trial of hormonal contraceptives among elite athletes (to control for healthy user effect) would be highly valuable.

An important finding of our systematic review is our conclusion that the current quality of evidence is very low. Despite 21 studies published to date, including 68,758 participants, methodological shortcomings limited the confidence in their findings. Our review identified problems with the assembly and maintenance of the cohort (lack of clarity or not including all participants who met eligibility criteria), lack of blinding of outcome assessors (eg, people performing Lachman test) to exposure, and considering and adjusting for important confounders such as excluding people with prior ACL injury, and/or those with a history of smoking, known collagen disorders, and diabetes; confirming ACL injury by magnetic resonance imaging; accounting for athletic status, age, and body mass index; and adjusting for medications such as corticosteroids. Addressing these important population, outcome measurement, and analytic factors is feasible in our judgment.

One of the continued and important challenges faced by investigators is the accurate assessment of menstrual cycle phase and hormonal evaluation. A recent population-based study revealed that more than one-third of women with normal cycle length were anovulatory.[41] Methods used to obtain hormone levels varied from serum, urine, and saliva and varied in timing of evaluations; in addition, for some studies the levels were not consistent with expected peak levels in threshold or timing, suggesting that some women might not have had ovulatory cycles (this would not be unusual for elite athletes) or were in a different phase than expected. The ideal study would evaluate serum hormonal levels on a regular basis over longer than a single cycle in order to account for cycle differences.

There are additional factors to consider for laxity assessment. Studies have suggested that Lachman testing measurements vary based on temperature and repeated measurements, with the least laxity being reported in the first examination and plateauing after repeated measures (thought possible because of learned relaxation after initial test). Extending the evaluation over a longer time frame would help account for these effects. Finally, studies of hormonal contraception focused exclusively on combined OCs and not newer progesterone-only options. Given that the timing of injury and laxity appears to coincide with the estradiol peak, it is possible that the reason studies have not found a protective effect is because the contraceptives used contain estradiol. Studies comparing injury rates and/or laxity among girls and women using progesterone-only contraceptives are needed.

Our systematic review has several limitations. First, there are few fair- or good-quality studies in this field. Additionally, it is recognized that electronic searches miss up to half of potential studies. While this systematic review followed recommended strategies to identify additional studies, including searching reference lists of prior reviews, some studies may have been erroneously excluded. Because only published studies were included, publication bias could also have potentially affected our results. However, only 1 study published exclusively as an abstract was identified during our search, and including this report would not have changed the results.

In conclusion, the literature suggests that ACL laxity and risk of injury may be increased in the ovulatory phase of the menstrual cycle. However, given the rating of very low strength of evidence, additional studies are needed to address the concerns of bias and confounding identified in this review and meta-analysis.

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