Limited Evidence Suggests a Protective Association Between Oral Contraceptive Pill Use and Anterior Cruciate Ligament Injuries in Females: A Systematic Review

Kathleen Samuelson, ScM,[†] Ethan M. Balk, MD, MPH,[‡] Erika L. Sevetson, MS,[§] and Braden C. Fleming, PhD*[||¶]

Context: Female athletes aged 14 to 18 years are at particular risk for anterior cruciate ligament (ACL) injuries. Hormonal factors are thought to predispose them to this injury. Oral contraceptive pills (OCPs) might reduce ACL injury risk, although the literature appears controversial.

Objective: To evaluate the association between OCP use and ACL injuries in women. The secondary objective was to determine the rates of ACL injuries in the pre- and postovulatory phases of the menstrual cycle in OCP and non-OCP (NOCP) users.

Data Sources: Searches were performed across 4 reference databases (PubMed, CINAHL, Embase, Cochrane), abstracts from 6 specialty societies, ClinicalTrials.gov, and reference lists of relevant papers.

Study Selection: We included studies investigating the association between OCP use and ACL injuries in females of any age or the distribution of ACL injuries across the menstrual cycle in OCP and NOCP users.

Study Design: Systematic review.

Level of Evidence: Level 3.

Data Extraction: Data regarding study design, population characteristics, OCP details, outcome definitions, analytic methods, and results were extracted from the included studies. The methodological quality of each study was assessed using the Newcastle-Ottawa scale.

Results: The search yielded 1305 citations, of which 7 retrospective observational studies met the inclusion criteria. Two large case-control studies with higher methodological quality suggested that OCP use may reduce the risk of sustaining an ACL injury. Five comparative studies examining injury distribution across the menstrual cycle in OCP and NOCP users had conflicting findings, were heterogeneous, and were limited by low methodological quality.

Conclusion: The evidence suggests OCP use may reduce the risk of ACL injury; however, no conclusions can be drawn regarding differences in risk of ACL injuries between OCP and NOCP users across the menstrual cycle. Studies were limited by small sample sizes, heterogeneity, and methodological concerns.

Keywords: ACL; injury; risk; hormones; oral contraceptives; systematic review

From the [†]Department of Molecular Pharmacology, Physiology, and Biotechnology, Brown University, Providence, Rhode Island, [‡]Center for Evidence Synthesis in Health, Brown University School of Public Health, Providence, Rhode Island, [§]Health and Information Services, Brown University Library, Brown University, Providence, Rhode Island, [||]Department of Orthopaedics, Warren Alpert Medical School of Brown University/Rhode Island Hospital, Providence, Rhode Island, and [¶]School of Engineering, Brown University, Providence, Rhode Island

*Address correspondence to Braden C. Fleming, PhD, Bioengineering Labs, Coro West, Suite 404, Rhode Island Hospital, 1 Hoppin Street, Providence, RI 02903 (email: braden_fleming@brown.edu).

The following author(s) declared potential conflicts of interest: This study was supported by the Lucy Lippitt Endowment.
DOI: 10.1177/1941738117734164

Approximately 1.4 million "noncontact" anterior cruciate ligament (ACL) tears occur annually worldwide.[17,31] The highest incidence occurs in female athletes aged 14 to 18 years.[28] There is currently no definitive explanation for the higher rate of ACL injuries in females.[12] Recent attention to hormonal risk factors is based on the known effects of ovarian steroid hormones on ligament and tendon properties,[16,20] the monthly circadian fluctuations of serum hormone concentrations,[5] and that these fluctuations are modulated when using oral contraceptive pills (OCPs).[25]

The prevalence of OCP use among female athletes has been estimated at 40% to 50%.[6,35] Because of the general acceptance of OCPs by female athletes,[4] the rising number of ACL injuries in the athletic population,[18] and the possible benefits of OCP use on sports performance,[27] further investigation into the preventative effect of OCP use against ACL injuries is essential.

Möller-Nielsen and Hammar[23] reported that soccer players who use OCPs have less traumatic injuries compared with non-OCP (NOCP) players, and suggested a causal association between premenstrual symptoms and injuries. In women who reported premenstrual symptoms, injury rates were greater during the premenstrual and menstrual periods. When the authors separated women by contraceptive status, a pattern of injury risk during the premenstrual and menstrual phases was not evident among women using OCPs.[22,23] However, this study was not specific to ACL injuries.

The current literature relating OCPs to soft tissue injury risk appears equivocal, and no causal associations between OCP use and ACL injury have been established. There are many potential factors that need to be considered when designing a study to establish the relationship between OCP use, the menstrual cycle, and ACL injury risk. The menstrual cycle (duration and magnitude) is highly variable across individuals. The cycle can be divided into 2 or 3 phases or evaluated by cycle day. Self-reported menstrual history is required to establish the timing of injury relative to the menstrual cycle. However, exclusively using self-reported information (eg, date of prior onset of menses) is less reliable than using other methods such as hormone measurements.[32] Menstrual dysfunction is not uncommon in athletic women.[3] Details regarding contraceptive use, including confirmed use at the time of injury, duration of use prior to injury, and contraceptive type (eg, oral vs non-oral hormonal-based contraceptive), are also important considerations. In addition, ACL injury verification may vary across studies, as not all ACL injuries result in reconstruction.[34] Given the number of factors and covariates that may affect ACL injury risk, large sample sizes are a necessity. Thus, an evidence-based review pooling existing studies could potentially provide valuable insight into the effects of OCP use on ACL injury risk. A confirmed prophylactic effect could have an enormous impact on ACL injury prevention strategies.

The primary objective of this systematic review was to evaluate the association between OCP use and ACL injuries in women. The secondary objective was to determine the rates of ACL injuries in the pre- and postovulatory phases of the menstrual cycle in OCP and NOCP users.

METHODS

This systematic review was based on PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) standards.[21]

Study Eligibility Criteria

Articles that investigated the key question and subquestion were included: those that evaluated an association between OCP use and ACL injuries in females of any age, and those that investigated the distribution of ACL injuries across the menstrual cycle in OCP and NOCP users. Studies did not need to necessarily specify the injury mechanism (eg, noncontact or contact) or severity (eg, partial or complete tear/rupture). However, they were required to include ACL injuries that occurred only after the start of OCP use. Studies did not need to characterize OCP exposure among the cohort deemed OCP users (eg, recent use, cumulative duration of use, dosage, and formulation). Clinical endpoints of interest included ACL injury diagnosed via clinical or imaging examination or documented ACL reconstruction surgery. All study designs were eligible, regardless of sample size.

Literature Searches

A literature search was performed in collaboration with 2 reference librarians at Brown University on December 2, 2016. Searches were conducted in 4 electronic databases: PubMed, Cumulative Index of Nursing and Allied Health Literature (CINAHL), Embase, and the Cochrane Central Trials Registry. Search strategies (see Appendix 1, available in the online version of this article) included terms for ACL, knee, and athletic injuries crossed with terms for oral contraceptives, hormones, and the menstrual cycle. Searches were not restricted by language or publication dates. A search for unpublished literature was performed in ClinicalTrials.gov and among abstracts since 2000 from 6 seminal research societies: American Orthopaedic Society for Sports Medicine, Orthopaedic Research Society, American College of Sports Medicine, Society for Endocrinology, American Association of Clinical Endocrinologists, and the European Society of Endocrinology. Reference lists from existing systematic reviews on ACL injury risk and included studies were also screened.

Literature Screening

A single researcher (K.S.) screened abstracts using the open-source software, Abstrackr (www.abstrackr.cebm.brown.edu).[37] Potentially eligible articles were exported into an evidence map to collect bibliographic information, study design, population characteristics, study duration, exposure, intervention, and reported outcomes. The primary exposure of interest was the protection factor, OCP. The secondary exposure of interest was

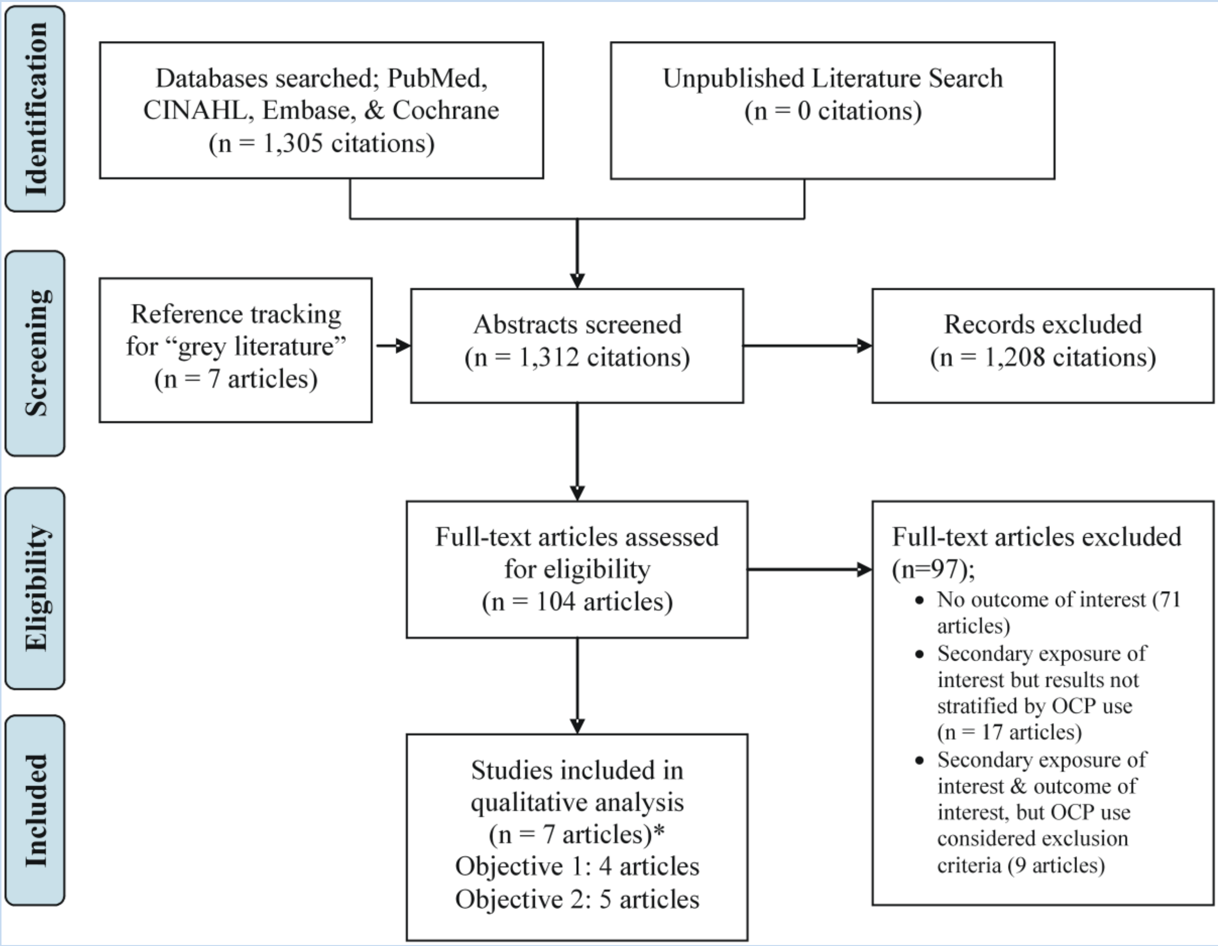

Figure 1. Literature flow based on the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. The flowchart was adapted from Moher et al[21] (http://www.prisma-statement.org). *Two of the 7 studies evaluated both the association (objective 1) and timing of injury (objective 2).

the risk factor, menstrual cycle. The outcome of interest was ACL injury (ie, noncontact or unspecified injury mechanism).

Data Extraction

Data from eligible studies were extracted into an a priori–designed data extraction form that included bibliographic information, study characteristics (eg, study design), population and intervention (OCP) characteristics, outcome definitions, baseline characteristics, results, and methodological quality.

Methodological Quality (Risk of Bias) Assessment

We assessed the methodological quality of observational studies with the validated Newcastle-Ottawa Scale (NOS).[38] The NOS assesses bias with regard to the selection of participants, comparability of study groups, and ascertainment of the exposure/outcome of interest. We adapted the rubrics for case-control studies and for cohort studies (see Appendix 2, available in the online version of this article). Studies were assessed to have low, high, or unclear risks of bias for each question.

RESULTS

The search yielded 1305 citations, of which 7 retrospective observational studies met the inclusion criteria (Figure 1): 3 case-control,[14,26,29] 1 cross-sectional,[40] and 3 longitudinal comparative studies.[1,2,19] Four studies investigated the association between OCP use and ACL injury (objective 1)[1,14,26,29]; 5 studies assessed the timing of ACL injury in OCP and NOCP users over the menstrual cycle (objective 2).[1,2,19,29,40] Two of these studies evaluated both the association and timing of injury.[1,29]

Overall, the study designs and analyses were heterogeneous (Table 1). Studies varied greatly in population size (range, 65-51,276 females), data collection methods (eg, self-report questionnaire, hormone metabolite measurements via urine

Table 1. Study design summary[a]

Study	Study Design	Country	N	Sport/ Level of Sport	Age, y (Mean ± SD; Range; Median)	Definition of OCP User	OCP vs NOCP Users	Outcome of Interest and Diagnosis	Data Collection Methods
Association studies									
Gray et al[14] (2016)	Case-control	USA	51,276 (12,819 cases, 38,457 controls)	Not reported	*Cases:* 24.1 ± 8.1 *Controls:* 24.1 ± 8.1	Prescription for OCP redeemed within the 12 months prior to index date ascertained from prescription drug database. Classified by any use, duration of use, dosage, and formulation	*Cases:* OCP 2999 (23.4%), NOCP 9820 (76.6%) *Controls:* OCP 8775 (22.8%), NOCP 29,682 (77.2%)	ACL or PCL reconstruction (n = 12,819); ICD-9-CM diagnosis codes	Commercial insurance database
Rahr-Wagner et al[26] (2014)	Case-control	Denmark	13,355 (4,497 cases, 8,858 controls)	Not reported	*Cases:* 24.0 (median), 17.1-37.9 (IQR). *Controls:* 23.7 (median), 17.0-37.7 (IQR)	Prescription for OCP redeemed within 5 years up to index date. Exposure set from prescription registry. Classified by any use, recent use, and cumulative duration of use	*Cases:* OCP 2047 (45.5%), NOCP 2450 (54.5%) *Controls:* OCP 4218 (47.5%), NOCP 4640 (52.4%)	Primary ACL reconstruction (n = 4497); reconstruction in knee registry was validated as proxy for injury	5 national Danish registries
Timing of injury studies									
Arendt et al[2] (2002)	Retrospective; longitudinal comparative	USA	83	*1996-1998:* NCAA and NAIA athletes (no further specifications). *1998-1999:* NCAA and NAIA basketball players	Not reported	OCP use within year prior to injury	OCP 25 (30.1%), NOCP 58 (69.9%)	ACL injury (n = 83); certified athletic trainer	NCAA ISS and independent contacts with certified NCAA and NAIA trainers
Lefevre et al[19] (2013)	Retrospective; longitudinal comparative	France	172	Recreational alpine skiers	34 ± 8.7	Undefined. Classified by dosage and formulation	OCP 53 (30.8%), NOCP 119 (69.2%)	ACL tear (n = 172); clinical examination by physician at ski resort	Questionnaire

(continued)

Table 1. (continued)

Study	Study Design	Country	N	Sport/ Level of Sport	Age, y (Mean ± SD; Range; Median)	Definition of OCP User	OCP vs NOCP Users	Outcome of Interest and Diagnosis	Data Collection Methods
Wojtys et al[40] (2002)	Retrospective; cross-sectional	USA	65	Skiers; nonskiers (no further specifications)	*General population:* 28 ± 10 (range, 15-56) *Skiers:* 32.1 ± 9.3 *Nonskiers:* 23.3 ± 7.8	Undefined	OCP 14 (21.5%), NOCP 51 (78.5%)	Acute ACL injury (n = 65); undefined	Questionnaire; hormone metabolite measurement via urine assay
Both association and timing of injury studies									
Agel et al[1] (2006)	Retrospective; longitudinal comparative	USA	3150	*2000-2001:* NCAA basketball players *2001-2002:* NCAA basketball and soccer players	Not reported	OCP use for entire season of play. Classified by dosage	OCP 906 (28.8%), NOCP 2244 (71.2%)[b]	ACL injury (n = 45) and ankle sprain (n = 116); certified athletic trainer or team physician	Contacts with certified athletic trainers at NCAA schools
Ruedl et al[29] (2009)	Case-control	Austria	186 (93 cases, 93 controls)	Recreational Alpine skiers	*Cases:* 38.8 ± 7.9 (range, 14-53) *Controls:* 38.1 ± 6.6 (range, 28-56)	Undefined. Collected information on “frequency” of use (did not specify further)	*Cases:* OCP 32 (34.4%), NOCP 61(65.6%) *Controls:* OCP 33 (35.5%), NOCP 60 (64.5%)	ACL injury (n = 93); MRI	Questionnaire

ACL, anterior cruciate ligament; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; IQR, interquartile range; MRI, magnetic resonance imaging; NAIA, National Association of Intercollegiate Athletics; NCAA, National Collegiate Athletic Association; NCAA ISS, NCAA Injury Surveillance System; NOCP, non–oral contraceptive pill; OCP, oral contraceptive pill; PCL, posterior cruciate ligament.
[a]Note that studies are presented according to their aim(s).
[b]Agel et al[1] did not explicitly state the overall number of OCP and NOCP users. These estimates were calculated from data presented within the article.

assay, or commercial insurance database), participant athletic status (eg, type of sport and level of activity), clinical endpoint for ACL injury (ie, explicit definition of clinical endpoint and diagnosis), and statistical estimates used to report findings.

Two case-control studies were at a lower risk of bias (Table 2).[14,26] The third case-control study was deemed to be of greater risk due to the lack of adjustments for confounders and ascertainment of OCP use.[29] The cross-sectional[40] and 3 longitudinal comparative cohort studies[1,2,19] were determined to be at greater risk of bias because of their representativeness of OCP users and no adjustments for confounders. It was unclear whether OCP users had used OCPs for at least 3 consecutive months prior to injury in the 4 studies[1,2,19,40] and whether ACL injury occurred prior to OCP use in 3 of those studies.[2,19,40] The case-control studies of Rahr-Wagner et al[26] and Gray et al[14] were deemed to possess the greatest methodological quality.

Studies Investigating the Association Between OCP Use and ACL Injury

The most recent case-control study by Gray et al[14] aimed to determine whether OCP use conferred a protective effect against the need for ACL reconstruction in women from an insurance provider database spanning an 11-year period (see Table 1). The outcome of interest was ACL or posterior cruciate ligament reconstruction in 12,819 women (age range, 15-39 years) who were enrolled in the database for at least 12 months prior to the surgical date. The control population (n = 38,457), which did not undergo surgery, was matched 3:1 by age and region. OCP use was defined as redeeming a prescription within the 12 months prior to the index date and was further characterized with regard to any use, duration of use (≥90 days or <90 days), dosage (monophasic or triphasic), and formulation (progesterone only or combined estrogen and progesterone). Several covariates and confounders were considered (asthma; type 1 diabetes; injectable, oral, or inhaled corticosteroids or antibiotics; comorbidities; previous lower extremity injuries; OCP dosage; and OCP formulation). Injury data were stratified into five, 5-year age groups for cases and controls. Conditional logistic regression determined that the cases in the 15- to 19-year-old age group were less likely to have used OCPs than controls (adjusted odds ratio [OR], 0.82; 95% CI, 0.75-0.91) (Table 3). The opposite was true for patients 25 to 34 years of age. No power analysis was presented.

Likewise, the case-control study by Rahr-Wagner et al[26] evaluated the association between OCP use and likelihood of undergoing ACL reconstruction injury in patients over a 6-year study period (see Table 1). The case population consisted of 4497 women who underwent ACL reconstruction. The control population was matched 2:1 by age and consisted of 8858 women who did not undergo reconstruction. OCP use was defined as redeeming a prescription for OCPs within the 5 years leading up to the index date and was further characterized with regard to any use, recent use, and cumulative use within a 5-year look-back period from the index date. The authors accounted for several confounders (age, immigrant status, obesity, pregnancy/birth, nonsteroidal anti-inflammatory drugs, and gross income). Raw injury data were stratified by 5-year age groups. Conditional logistic regression determined that ever users (adjusted OR, 0.82; 95% CI, 0.75-0.90), recent users (adjusted OR, 0.81; 95% CI, 0.72-0.89), and long-term users (adjusted OR, 0.80; 95% CI, 0.74-0.91) had significantly lower likelihoods of undergoing ACL reconstruction compared with never users (Table 3).[26] The authors found no dose-dependent association between cumulative duration of OCP use and the likelihood of undergoing ACL reconstruction, though a trend was noted. No power analysis was presented.

Ruedl et al[29] performed a case-control study investigating the influence of OCP use on ACL injury risk in female recreational skiers (see Table 1). The case population consisted of 93 injured skiers over the course of 2 winter seasons at an Austrian ski resort. The control population was matched 1:1 by age and randomly selected from the same resort. OCP exposure was ascertained by a self-report questionnaire, though OCP use was undefined. Using chi-square analysis, the authors found no significant difference in OCP use at the time of injury between cases and controls (34.4% and 35.5%, respectively), and they concluded there was no protective association between OCP use and ACL injuries in skiers (Table 3).[29] A power analysis determined that the study was adequately powered (90%).

The longitudinal comparative study by Agel et al[1] sought to determine whether OCP use conferred a protective effect against ACL and ankle injuries (see Table 1). Hormonal therapy status (defined as continuous use over the course of a season) of 3150 female National Collegiate Athletic Association (NCAA) athletes (basketball and soccer players) across 2 seasons was determined. OCP dosage was classified (monophasic or triphasic). The NOCP arm of this study included women on nonoral hormonal-based contraceptives. Using chi-square analysis, the authors reported no protective association between hormonal therapy use and ACL or ankle injuries (Table 3).[1] While the study provided insight into injury rates by sport, it was inadequately powered to evaluate the effect of OCP use on ACL injury risk.

Studies Investigating the Timing of ACL Injury Over the Menstrual Cycle

Lefevre et al[19] performed a longitudinal comparative study over 1 season across 8 Alpine ski resorts to assess the distribution of ACL tears across the menstrual cycle in female skiers and investigate OCP use within this population (see Table 1). OCP use was generally undefined except for dosage and formulation. A total of 172 injured females were included in the analysis (53 OCP users, 119 NOCP users). The NOCP arm included women on nonoral hormonal-based contraceptives. Women were excluded if their prior onset of menses was greater than 30 days before injury or if their menstrual cycle was irregular. Self-reported date of prior onset of menses was used to determine cycle phase at the time of injury. The authors reported the menstrual cycle as 3 phases for the combined group analysis and 2 phases for the subpopulation (OCP vs NOCP) analyses.

Table 2. Newcastle-Ottawa Scale (NOS) quality (risk of bias) assessment

Study	Study Design	A1	A2	A3	A4	B1	C1	C2	C3	D1	D2	D3	D4	E1	F1	F2	F3
Studies evaluated with the NOS case-control rubric (items A1-C3)[a]																	
Gray et al[14] (2016)	Case-control	Low	Low	Low	Low	Low	Low	Low	Low								
Rahr-Wagner et al[26] (2014)	Case-control	Low	Low	Low	Low	Low	Low	Low	Low								
Ruedl et al[29] (2009)	Case-control	Low	Low	Low	Low	High	High	Low	Low								
Studies evaluated with the NOS cohort rubric (items D1-F3)[b]																	
Agel et al[1] (2006)	Longitudinal comparative									High	Low	Unclear	Low	High	Low	Unclear	Low
Arendt et al[2] (2002)	Longitudinal comparative									High	Low	Unclear	Unclear	High	Low	Unclear	Low
Lefevre et al[19] (2013)	Longitudinal comparative									High	Low	High	Unclear	High	Low	Unclear	Low
Wojtys et al[40] (2002)	Cross-sectional									High	Low	High	Unclear	High	Unclear	Unclear	Low

[a]Case-control rubric (items A1-C3): Selection (A1, case definition; A2, representativeness of cases; A3, selection of controls; A4, definition of controls). Comparability (B1, comparability of cases and controls on the basis of design or analysis). Exposure (C1, ascertainment of exposure; C2, same method of ascertainment for cases and controls; C3, nonresponse rate).

[b]Cohort rubric (Items D1-F3): Selection (D1, representativeness of exposed cohort; D2, selection of the nonexposed cohort; D3, ascertainment of exposure; D4, demonstration that outcome of interest was not present at start of study). Comparability (E1, comparability of cohorts on basis of the design or analysis). Outcome (F1, assessment of outcome; F2, was follow-up long enough for outcomes to occur; F3, adequacy of follow-up cohorts). Details are provided in Appendix 2.

Table 3. Results from studies that investigated the association between OCP use and ACL injury

Study	Adjustment for Covariates and/or Confounders	Sensitivity Analysis	Injury/Reconstruction Rates Stratified by Age	Key Findings From Association Analysis	Dose-Dependent Analysis
Agel et al[1] (2006)	NR	NR	NR	No significant difference in injury rates between hormonal therapy users and non-hormonal therapy users across the 2 years. Association between OCP use and ACL injury could not be determined.	NR
Gray et al[14] (2016)	Six covariates and 2 confounders. Cases were approximately 3 times more likely to have previous lower extremity injuries and 2 times more likely to receive a steroid injection than controls. Cases were more likely to use triphasic OCP compared with controls.	The analysis yielded statistically different estimates of the OR between different durations of use (≤90 d and <90 d).	Women in age group 15-19 years had the highest incidence of ACL reconstruction (45.69% of cases), and a majority of these reconstructions occurred in women between the ages of 15 and 18 years.	Cases in the age group 15-19 years were significantly less likely to have used OCPs than controls. OCP users in this age group underwent 18% fewer reconstructions than NOCP users.	NR
Rahr-Wagner et al[26] (2014)	Six confounders. NSAID drug use and higher gross income were more common among cases. Obesity, pregnancy/birth, and immigrant status were more common among controls.	Three analyses yielded similar estimates of the OR as the main analysis if multiple imputation was not used, there was poor medication adherence, and cases were not actually on OCPs at the time of injury.	Women in the age group >15 and ≤ 20 years had the highest incidence of ACL reconstruction (31.8% of cases).	Compared with never users (reference group), ever users, recent users, and long-term users had significantly lower likelihoods of undergoing ACL reconstruction.	No significant dose-dependent association between OCP use for all 5 cumulative durations and likelihood of undergoing ACL reconstruction—only a slight trend toward a dose-dependent relationship.
Ruedl et al[29] (2009)	NR	NR	NR	No significant difference in OCP use on day of injury/questioning between cases and controls.	NR

ACL, anterior cruciate ligament; NOCP, non–oral contraceptive pill; NR, not reported; NSAID, nonsteroidal anti-inflammatory drug; OCP, oral contraceptive pill; OR, odds ratio.

Chi-square analysis determined that a majority of OCP users and NOCP users were injured during the preovulatory phase of the cycle (67.9% and 71.4%, respectively), though there was no significant difference in tear rates between them (Table 4).[19] No power analysis was presented.

The case-control study by Ruedl et al[29] was designed to compare the frequencies of ACL injuries in the pre- and postovulatory phases of the menstrual cycle (see Table 1) and included 93 cases (32 OCP users, 61 NOCP users) and 93 controls (33 OCP users, 60 NOCP users). Cycle phase was determined using self-reported date of prior onset of menses. Chi-square analysis determined no statistical difference in injury distribution between the pre- and postovulatory phases across case and control NOCP users ($P = 0.08$).[29] There was a trend suggesting that NOCP users were 1.88 times more likely to injure their ACL in the preovulatory phase of the menstrual cycle, though this was not significant (Table 4). The study was underpowered to make final conclusions.

The study by Agel et al[1] was designed to evaluate the incidence of injury over the menstrual cycle (see Table 1). Periodicity was defined as a pattern that could be identified over a given time frame and repeated over several time frames. Of the 3150 females included, 906 were OCP users and 2244 were NOCP users. Athletes were excluded if they reported more than 28 days between either time of injury and prior onset of menses, time of injury and next onset of menses, or if their contraception status was classified as “other” (nonoral hormonal-based contraceptive users, women who changed their contraceptive status over the course of the season, or women who quit the team). There were 26 OCP users (8 ACL injuries, 16 ankle injuries) and 30 NOCP users (12 ACL injuries, 18 ankle injuries) included in this analysis. To analyze raw injury distribution data, periodicity analyses were conducted using a centered moving average with a span of 4 days and a nonlinear regression analysis with bootstrap estimation of the confidence intervals. While no periodicity was found in OCP users whose timing of injury was determined using either prospective or retrospective assessment of menses onset, periodicity was found among NOCP users whose timing of injury was determined using retrospective data collection, with the peak occurrence of injury between days 7 and 9 of the menstrual cycle (follicular phase) (Table 4).[1] No power analysis was provided.

Arendt et al[2] also performed a longitudinal comparative study to analyze the 28-day periodicity of ACL injuries in female athletes using and not using OCPs (see Table 1). Data were collected from the NCAA Injury Surveillance System (ISS) over 2 NCAA seasons. OCP use was self-reported and defined as “current use” or “any use” within the year leading up to injury. A total of 83 injured females (25 OCP users, 58 NOCP users) were included. Female athletes were excluded if they did not have at least 10 to 12 menstrual cycles per year or if their most recent menstrual cycle prior to injury lasted for more than 28 days. Investigators used self-reported date of prior menses to determine cycle phase at time of injury. The authors subdivided the menstrual cycle into phases, using 2 separate phase classification schemes (days 1-9, 10-14, and 15-28; days 1-7, 8-14, 15-21, and 22-28). All analyses were normalized to a 28-day menstrual cycle. Using chi-square analyses for OCP and NOCP users,[2] there were no significant associations between injury distribution and cycle phase with either phase classification scheme (Table 4). However, there was significant variation in the number of injuries by cycle day in both groups, with the greatest number of injuries occurring at the beginning of the cycle. The location of the high-risk time interval for OCP users was reported to be “earlier in the cycle” than it was for NOCP users, though the exact location of the “high-risk time interval” was not determined. No power analysis was provided.

Wojtys et al[40] sought to determine whether an association existed between the menstrual cycle phase and distribution of ACL injuries (see Table 1). High school and college female athletes were recruited within 24 hours of injury over a 2-year period. A questionnaire was used to determine OCP use, though no definition of OCP use was specified. Women with irregular cycles or missed menstrual cycles were excluded. A total of 65 injured females (14 OCP users, 51 NOCP users) were included. Self-reported date of prior onset of menses and hormone assay via urine sample were used to determine cycle phase at time of injury. The authors classified the menstrual cycle by 3 phases (follicular phase, ovulatory phase, luteal phase) and used chi-square analysis to determine that there was no significant association between ACL injury distribution and menstrual cycle phase in OCP users (Table 4). However, a significant association between the distribution of ACL injuries and menstrual cycle phase was found in NOCP users ($P < 0.001$), in which 47% of injuries were observed during the ovulatory phase—2.5 times the expected number (14%). A power analysis based on 80% power to detect an effect size of 0.40 suggested adequate sample size. Since the number of women using OCPs was low ($n = 14$), the study was not powered to determine whether OCP use contributed to the lower rate of injuries during the ovulatory phase in OCP users compared with NOCP users.

DISCUSSION

The systematic review identified 7 studies that targeted the 2 study objectives. Overall, 2 of the 4 studies relevant to the first objective (associations between OCP use and ACL injuries) concluded that there is an association between OCP use and a reduction of ACL injuries. These 2 studies[14,26] demonstrated that young women (15-20 years old) using OCPs underwent fewer ACL reconstructions compared with a matched control group. In contrast, the other 2 studies,[1,29] which were determined to be of lower quality, did not report differences in ACL injuries with OCP use. The 5 studies[1,2,19,29,40] pertaining to the second objective (varying rates of ACL injuries over the course of the menstrual cycle in OCP and NOCP users) were, overall, inconclusive due to limited sample sizes and greater risk of bias.

The 2 higher-quality case-control studies[14,26] addressing the first objective used large sample sizes and adjusted for covariates and confounders, though neither fully addressed the

Table 4. Results from studies that investigated the timing of injury over the menstrual cycle

Study	Menstrual Cycle Division	Analysis on Timing of Injury in Combined Group	Analysis on Timing of Injury in OCP Users	Analysis on Timing of Injury in NOCP Users
Agel et al[1] (2006)	NR	NR	No periodicity in injury distribution of OCP users whose timing of injury was calculated using recall or prospective data collection.	Periodicity demonstrated in injury distribution of NOCP users whose timing of injury was calculated using recall. Highest number of injuries occurred between days 7 and 9 of the follicular phase. No periodicity in NOCP users whose timing of injury was calculated using prospective data collection.
Arendt et al[2] (2002)	Two separate phase classifications: days 1-9, 10-14, and 15-28; days 1-7, 8-14, 15-21, and 22-28	No significant variation in injury distribution by cycle phase. Signification variation in distribution of injuries by cycle day. Greatest number of injuries occurred earlier in the cycle, although the exact location of the high- and low-risk intervals could not be determined. Generally, follicular phase was associated with a higher risk of injury, and luteal phase was associated with a lower risk of injury.	No significant variation in injury distribution by cycle phase. Significant variation in injury distribution by cycle day. Greatest number of injuries occurred at the beginning of the cycle. Compared with NOCP users, the location of the high-risk time interval was earlier in the cycle, although the exact location could not be determined.	No significant variation in injury distribution by cycle phase. Significant variation in injury distribution by cycle day. Greatest number of injuries occurred at the beginning of the cycle, although the exact location of the high-risk time interval could not be determined.
Lefevre et al[19] (2013)	Two separate phase classifications: follicular phase (days 1-9), ovulatory phase (days 10-14), and luteal phase (days 15-30); preovulatory (follicular and ovulatory) and postovulatory (luteal)	Significant association between injury distribution and menstrual phase. ACL injury was 2.4 times more likely in the preovulatory phase than the postovulatory phase.	Majority of OCP users (67.9%) were injured during the preovulatory phase. The rate of injury during the preovulatory phase was not significantly different with regard to OCP use.	Majority of NOCP users (71.4%) were injured during the preovulatory phase.
Ruedl et al[29] (2009)	Preovulatory phase and postovulatory phase	Cases were significantly more likely to be in the preovulatory phase at the time of injury than controls were at the time of questioning, which meant female skiers were 1.92 times more likely to tear their ACL in the preovulatory phase than the postovulatory phase.	NR	No statistical difference in cycle phase at time of injury/questioning—only a trend toward a 1.88 times increase in injuries during the preovulatory phase.
Wojtys et al[40] (2002)	Follicular phase (days 1-9), ovulatory phase (days 10-14), and luteal phase (days 15-28)	Significant association between injury distribution and menstrual phase, with more injuries than expected in the ovulatory phase.	No significant association between injury distribution and cycle phase—only a trend toward more injuries than expected in the ovulatory and luteal phases, and fewer injuries than expected in the follicular phase. OCP users sustained less injuries than NOCP users in the ovulatory phase (29% and 47%, respectively).	Significant association between injury distribution and cycle phase, with 2.5 times more injuries than expected in the ovulatory phase.

ACL, anterior cruciate ligament; NOCP, non–oral contraceptive pill; NR, not reported; OCP, oral contraceptive pill.

research question. Both used ACL reconstruction as a proxy for ACL injury. Adjusted analyses were performed to determine odds ratios. The age group that had the highest incidence of ACL reconstruction and that benefitted from OCP use was in agreement with that reported for the general female patient population (15-19 years).[13] The key findings of these 2 studies, however, are only generalizable to women who undergo ACL reconstruction. This is important to distinguish as not every woman who sustains an ACL injury will undergo surgery.[34] Furthermore, the authors could not gather information on a number of relevant lifestyle confounders such as athletic status, body mass index, smoking status, ethnicity, and cause of injury due to the sources used for data collection (large national registries and commercial insurance databases). It was also unclear whether these 2 studies were restricted to noncontact ACL injuries. As for the other 2 studies addressing the first objective,[1,29] the finding of no significant effect of OCP use on ACL injury risk was likely because of a number of factors, including the heterogeneity of the methods and the greater risks for bias, as determined by the NOS.[38] Therefore, it seems reasonable to assume that the differences in study quality may be responsible for the conflicting results of the studies addressing the first objective.

The study by Rahr-Wagner et al[26] was the only study to verify that women were using OCPs at the time of injury. Women who used OCPs at any point during the look-back period, women who used OCPs prior to the year leading up to the index date (but not within the year leading up to index date), and women who started using OCPs 1 year prior to the index date had a lower likelihood of undergoing ACL reconstruction.[26] The study by Gray et al[14] was the only study to adjust for type of OCP in analysis, specifically OCP dosage and formulation. They determined that injured females (cases) were significantly more likely to use OCPs for longer than 90 days and more likely to use triphasic OCPs compared with uninjured females (controls).

While the 5 studies examining the ACL injury distribution across the menstrual cycle (secondary objective) provide interesting data, heterogeneity across studies and risk of bias were the primary concerns. We initially included this question in this review to determine whether there was a statistical association between the menstrual cycle and noncontact ACL injuries in OCP and NOCP users so that conclusions could be drawn about the effect of OCP use on injury rates in these subpopulations. Unfortunately, there was little consistency in how the 5 studies classified the menstrual cycle in their analyses: 2 phases (preovulatory, postovulatory),[19,29] 3 phases (follicular, ovulatory, luteal),[19,40] or day intervals.[1,2]

Among the 2 studies[19,29] that divided the cycle into 2 phases, only Ruedl et al[29] conducted a separate analysis on the injury distribution for NOCP users. No comparisons could be made between ACL injury distribution for OCP and NOCP users. Furthermore, Ruedl et al[29] did not determine significance for NOCP users, only a trend to suggest that NOCP users have 1.88 times more ACL injuries during the preovulatory phase. Lefevre et al[19] did not find significance for either subgroup, though they reported that a majority of OCP and NOCP users were injured during the preovulatory phase.

Wojtys et al[40] divided the cycle into 3 phases and found no significant differences relating to the ACL injury distribution within OCP users. However, OCP users sustained fewer injuries during the ovulatory phase compared with NOCP users. No further conclusions could be drawn because the OCP group was too small to determine whether OCP use had an effect on injury rate. Among NOCP users, there was significant variation in injury distribution by cycle phase, with more than 2.5 times the expected number of injuries during the ovulatory phase.

Agel et al[1] classified the cycle by days and reported findings based on periodicity, which was defined as a pattern that could be identified over a given time frame and repeated over several time frames. They determined that periodicity did not exist among OCP users, so no comparisons were made between OCP and NOCP users. However, periodicity existed for NOCP users. The authors asserted that the greatest risk of injury in this subpopulation was between days 7 and 9 of the menstrual cycle, though the authors did not explicitly state whether this finding was significant.

Arendt et al[2] used ambiguous terms to report their findings on injury distribution across the menstrual cycle. The authors determined there was significant variation in injury distribution by cycle day for both OCP and NOCP users. OCP and NOCP users were at increased risk for sustaining injuries at the "beginning of the cycle." The high-risk period for OCP users was earlier in the cycle compared with the high-risk period for NOCP users, although the authors could not determine the exact location of the high-risk interval for either subgroup due to the multiple smoothing efforts (centered moving average and 2 regression models). The statistical models used by Arendt et al[2] seemed to fit the injury incidence data better than the statistical models used by Agel et al.[1] However, the small pooled sample sizes in both studies called into question the interpretation of these data.

Another major limitation of the studies evaluating the second objective was the determination of cycle length.[1,2,19,30,40] Self-reported methods are known not to be accurate for determining menstrual cycle length.[32] Four studies[1,2,19,40] also excluded women with abnormal cycle histories. However, many studies point to 28 days as the average length of the menstrual cycle.[7,8,11,32,33] There is a substantial body of literature demonstrating that both inter- and intraindividual variability in total cycle and phase lengths are normal in the general population.[7,8,11,15] Thus, using the results of 1 hormone assay to determine timing of injury, as was done in the study by Wojtys et al,[40] may also be a limitation. Furthermore, it is known that there is a greater prevalence of menstrual dysfunction among active women.[3,10,24,35] Subtle menstrual disturbances associated with exercise, including luteal-phase defect or anovulation, are also prevalent in this population[9,39] and not detectable using menstrual history questionnaires.[36] Therefore, these studies[1,2,19,40] may lack generalizability even across the athletic population. In addition, injury mechanism (eg, contact vs noncontact) was not clearly established in all articles. It is possible that the relationship between OCP use and injury risk could vary based on the mechanism of injury. Nonetheless, the majority of ACL injuries in female athletes are considered to be noncontact.[17]

There are other limitations inherent to this systematic review. Only 1 investigator (K.S.) performed the review. However, the search strategy and data interpretation were performed under the direction of a research professional in public health (E.M.B.) with extensive experience in performing systematic reviews. Another limitation is that the conclusions of a systematic review are only as strong as the studies comprising it. All 7 studies were nonrandomized, and only 2 of them adjusted for covariates and confounders.[14,26] Several of the studies were either inadequately powered to draw definitive conclusions[1,40] or did not report power.[2,19] Low methodological quality (ie, high risk of bias) was determined using the NOS for 4 of the 7 studies included (see Table 2).[1,2,19,40] Documentation of ACL injury, menses onset, cycle definition, and other covariates were not consistent between studies. Furthermore, the mechanisms of ACL injury among skiers (3 studies[19,29,40]) are different from those experienced by athletes participating in team sports. The mean age of skiers sustaining ACL injuries is also greater.[14,29] An additional discrepancy between the studies was the designation of OCP versus NOCP users. Studies differed in whether they provided a clear definition of what it meant to be called an OCP user and whether OCP use was further classified (eg, any use vs never use, duration of use, recent use, OCP formulation, or OCP dosage). With regard to the NOCP arm, studies differed as to whether they delineated NOCP users as having ever or never used OCPs and whether NOCP users were on nonoral hormonal-based contraceptives at time of injury.

CONCLUSION

Limited evidence from the 2 studies with greater methodological quality suggests OCP use may reduce the risk of sustaining an ACL injury. However, injury distribution findings across the menstrual cycle between OCP and NOCP users do not support a protective effect, largely because of heterogeneity of the studies and risk of study bias. A better understanding of the relationship between OCP use and ACL injury risk is warranted.

ACKNOWLEDGMENT

The authors acknowledge the contribution of Gaelen P. Adam (Center for Evidence Synthesis in Health, Brown University School of Public Health).

REFERENCES

1. Agel J, Bershadsky B, Arendt EA. Hormonal therapy: ACL and ankle injury. *Med Sci Sports Exerc*. 2006;38:7-12.
2. Arendt EA, Bershadsky B, Agel J. Periodicity of noncontact anterior cruciate ligament injuries during the menstrual cycle. *J Gend Specif Med*. 2002;5:19-26.
3. Beals KA, Hill AK. The prevalence of disordered eating, menstrual dysfunction, and low bone mineral density among US collegiate athletes. *Int J Sport Nutr Exerc Metab*. 2006;16:1-23.
4. Bennell K, White S, Crossley K. The oral contraceptive pill: a revolution for sportswomen? *Br J Sports Med*. 1999;33:231-238.
5. Beynnon BD, Bernstein IM, Belisle A, et al. The effect of estradiol and progesterone on knee and ankle joint laxity. *Am J Sports Med*. 2005;33:1298-1304.
6. 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;76:873-878.
7. Cole LA, Ladner DG, Byrn FW. The normal variabilities of the menstrual cycle. *Fertil Steril*. 2009;91:522-527.
8. Creinin MD, Keverline S, Meyn LA. How regular is regular? An analysis of menstrual cycle regularity. *Contraception*. 2004;70:289-292.
9. De Souza MJ, Miller BE, Loucks AB, et al. High frequency of luteal phase deficiency and anovulation in recreational women runners: blunted elevation in follicle-stimulating hormone observed during luteal-follicular transition. *J Clin Endocrinol Metab*. 1998;83:4220-4232.
10. De Souza MJ, Williams NI. Physiological aspects and clinical sequelae of energy deficiency and hypoestrogenism in exercising women. *Hum Reprod Update*. 2004;10:433-448.
11. Fehring RJ, Schneider M, Raviele K. Variability in the phases of the menstrual cycle. *J Obstet Gynecol Neonatal Nurs*. 2006;35:376-384.
12. Gornitzky AL, Lott A, Yellin JL, Fabricant PD, Lawrence JT, Ganley TJ. Sport-specific yearly risk and incidence of anterior cruciate ligament tears in high school athletes: a systematic review and meta-analysis. *Am J Sports Med*. 2016;44:2716-2723.
13. Granan LP, Bahr R, Steindal K, Furnes O, Engebretsen L. Development of a national cruciate ligament surgery registry: the Norwegian National Knee Ligament Registry. *Am J Sports Med*. 2008;36:308-315.
14. Gray AM, Gugala Z, Baillargeon JG. Effects of oral contraceptive use on anterior cruciate ligament injury epidemiology. *Med Sci Sports Exerc*. 2016;48:648-654.
15. Harlow SD, Ephross SA. Epidemiology of menstruation and its relevance to women's health. *Epidemiol Rev*. 1995;17:265-286.
16. Hart DA, Archambault JM, Kydd A, Reno C, Frank CB, Herzog W. Gender and neurogenic variables in tendon biology and repetitive motion disorders. *Clin Orthop Relat Res*. 1998;351:44-56.
17. Hewett TE, Myer GD, Ford KR. Anterior cruciate ligament injuries in female athletes: part 1, mechanisms and risk factors. *Am J Sports Med*. 2006;34:299-311.
18. Kaeding CC, Leger-St-Jean B, Magnussen RA. Epidemiology and diagnosis of anterior cruciate ligament injuries. *Clin Sports Med*. 2017;36:1-8.
19. Lefevre N, Bohu Y, Klouche S, Lecocq J, Herman S. Anterior cruciate ligament tear during the menstrual cycle in female recreational skiers. *Orthop Traumatol Surg Res*. 2013;99:571-575.
20. Liu SH, al-Shaikh R, Panossian V, et al. Primary immunolocalization of estrogen and progesterone target cells in the human anterior cruciate ligament. *J Orthop Res*. 1996;14:526-533.
21. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol*. 2009;62:1006-1012.
22. Möller Nielsen J, Hammar M. Sports injuries and oral contraceptive use. Is there a relationship? *Sports Med*. 1991;12:152-160.
23. Möller-Nielsen J, Hammar M. Women's soccer injuries in relation to the menstrual cycle and oral contraceptive use. *Med Sci Sports Exerc*. 1989;21:126-129.
24. Nichols JF, Rauh MJ, Lawson MJ, Ji M, Barkai HS. Prevalence of the female athlete triad syndrome among high school athletes. *Arch Pediatr Adolesc Med*. 2006;160:137-142.
25. Nose-Ogura S, Yoshino O, Yamada-Nomoto K, et al. Oral contraceptive therapy reduces serum relaxin-2 in elite female athletes. *J Obstet Gynaecol Res*. 2017;43:530-535.
26. Rahr-Wagner L, Thillemann TM, Mehnert F, Pedersen AB, Lind M. Is the use of oral contraceptives associated with operatively treated anterior cruciate ligament injury? A case-control study from the Danish Knee Ligament Reconstruction Registry. *Am J Sports Med*. 2014;42:2897-2905.
27. Rechichi C, Dawson B, Goodman C. Athletic performance and the oral contraceptive. *Int J Sports Physiol Perform*. 2009;4:151-162.
28. Renstrom PA. Eight clinical conundrums relating to anterior cruciate ligament (ACL) injury in sport: recent evidence and a personal reflection. *Br J Sports Med*. 2013;47:367-372.
29. Ruedl G, Ploner P, Linortner I, et al. Are oral contraceptive use and menstrual cycle phase related to anterior cruciate ligament injury risk in female recreational skiers? *Knee Surg Sports Traumatol Arthrosc*. 2009;17:1065-1069.
30. Ruedl G, Ploner P, Linortner I, et al. Interaction of potential intrinsic and extrinsic risk factors in ACL injured recreational female skiers. *Int J Sports Med*. 2011;32:618-622.
31. Samuelsson K. *Anatomic Anterior Cruciate Ligament Reconstruction—Current Evidence and Future Directions* [dissertation]. Gothenburg, Sweden: Sahlgrenska Academy, University of Gothenburg; 2012.

32. Small CM, Manatunga AK, Marcus M. Validity of self-reported menstrual cycle length. *Ann Epidemiol*. 2007;17:163-170.
33. Steiner MJ, Hertz-Picciotto I, Taylor D, Schoenbach V, Wheeless A. Retrospective vs. prospective coital frequency and menstrual cycle length in a contraceptive effectiveness trial. *Ann Epidemiol*. 2001;11:428-433.
34. Swirtun LR, Eriksson K, Renstrom P. Who chooses anterior cruciate ligament reconstruction and why? A 2-year prospective study. *Scand J Med Sci Sports*. 2006;16:441-446.
35. Torstveit M, 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;39:141-147.
36. Vescovi JD. The menstrual cycle and anterior cruciate ligament injury risk: implications of menstrual cycle variability. *Sports Med*. 2011;41:91-101.
37. Wallace BC, Small K, Brodley CE, Lau J, Trikalinos TA. Deploying an interactive machine learning system in an evidence-based practice center: Abstrackr. In: *Proceedings of the ACM SIGHIT International Health Informatics Symposium (IHI), Miami, Florida*. New York, NY: ACM; 2012:819-824.
38. Wells GA, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analysis. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed September 7, 2017.
39. Williams NI, Bullen BA, McArthur JW, Skrinar GS, Turnbull BA. Effects of short-term strenuous endurance exercise upon corpus luteum function. *Med Sci Sports Exerc*. 1999;31:949-958.
40. Wojtys EM, Huston LJ, Boynton MD, Spindler KP, Lindenfeld TN. The effect of the menstrual cycle on anterior cruciate ligament injuries in women as determined by hormone levels. *Am J Sports Med*. 2002;30:182-188.