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Anterior cruciate ligament laxity related to the menstrual cycle: an updated systematic review of the literature

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Objectives: *The purpose of this study was to conduct a systematic review regarding the purported differences in anterior cruciate ligament (ACL) laxity throughout the course of the menstrual cycle.*

Methods: *A systematic review was performed by searching electronic databases, along with hand-searching of journals and reference tracking for any study that assessed ACL integrity throughout the menstrual cycle from 1998 until 2011. Studies that met the pre-defined inclusion criteria were evaluated using the Modified Sackett Score (MSS) instrument that assessed their methodological quality.*

Results: *Thirteen articles out of a possible 28 met the inclusion criteria.*

Conclusions: *This systematic review found 13 clinical trials investigating the effect of the menstrual cycle on ACL laxity. There is evidence to support the hypothesis that the ACL changes throughout the menstrual cycle, with it becoming more lax during the pre-ovulatory (luteal) phase. Overall, these reviews found statistically significant differences for variation in ACL laxity and injury throughout the menstrual cycle, especially during the pre-ovulatory phase. Female athletes may need to take precautions in order to reduce the likelihood of ACL injury. However, the quality of the assessments was low and the evidence is still very limited. More and better quality research is needed in this area.*

KEY WORDS: ligament, laxity, menstrual

Objectifs : *Le but de cette étude était de procéder à un examen systématique concernant les prétendues différences dans le laxisme du ligament croisé antérieur (LCA) tout au long du cycle menstruel.*

Méthodologie : *Un examen systématique a été effectué en recherchant des bases de données électroniques, ainsi qu'en effectuant une recherche manuelle des revues et un suivi de références pour toute étude de 1998 jusqu'en 2011 qui a évalué l'intégrité du ligament croisé antérieur LCA tout au long du cycle menstruel. Les études qui répondaient aux critères d'inclusion prédéfinis ont été évaluées en utilisant le score modifié de Sackett (MSS) qui a évalué la qualité de leur méthodologie.*

Résultats : *Treize articles, sur un total possible de 28, répondaient aux critères d'inclusion.*

Conclusions : *Cet examen systématique a découvert 13 essais cliniques portant sur l'effet du cycle menstruel sur le laxisme du LCA. Il existe des preuves pour étayer l'hypothèse que le LCA change tout au long du cycle menstruel, devenant plus relâché lors de la phase pré-ovulatoire (lutéale). Dans l'ensemble, ces examens ont montré des différences statistiquement significatives entre la variation de laxisme et de blessures du LCA tout au long du cycle menstruel, en particulier pendant la phase pré-ovulatoire. Les athlètes de sexe féminin devraient peut-être prendre des précautions pour réduire le risque de blessures du LCA. Cependant, les évaluations qualitatives étaient insuffisantes et les preuves sont encore très limitées. Donc, il faut effectuer plus de recherches, et de meilleure qualité, dans ce domaine.*

MOTS CLÉS : ligament, laxisme, menstruel

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Introduction

The physical disability and long rehabilitation process associated with anterior cruciate ligament (ACL) injury can be both psychologically and financially devastating to the individual, ultimately resulting in a decreased quality of life.[1] Female athletes have a higher rate of ACL injury than do men, and many of these injuries require extensive surgical and rehabilitative interventions, with a financial burden to the American healthcare system estimated to approach $650 million annually.[1] Bearing that in mind, it is imperative to understand the mechanisms leading to such an injury in an effort to prevent its occurrence and its subsequent sequelae. Although both men and women are susceptible, the literature states that women have a 4 to 6 fold increased incidence of ACL injury.[2,3] Notwithstanding the fact that a definitive etiology for this discrepancy between the sexes has not been established, proposed theories to account for it include: neuromuscular and biomechanical factors (differences in pelvis width/increased Q-angles in females, smaller femoral notch widths in females, increased female hamstring flexibility, and imbalanced hamstrings-to-quadriceps strength leading to differences in landing patterns); psychological factors (women may be more prone to maladaptive perfectionism leading to overtraining and burnout) and nutritional differences (higher frequency of food restriction and decreased calcium intake among females compared to males).[1,3,4] An additional theory posits increased ligament laxity is related to hormonal fluctuations during the menstrual cycle.[1]

The menstrual cycle is controlled by the pituitary-hypothalamic-ovarian axis and involves the complex interaction of estrogen, progesterone, relaxin and testosterone.[1] Typically, each menstrual cycle spans 28 days, beginning with the follicular phase from days 1-9 during which estrogen predominates, followed by the ovulatory phase spanning days 10-14, where estrogen continues to prevail and reaches its peak.[1] The cycle ends with the luteal phase extending from days 15-28 during which time progesterone levels surpass that of estrogen levels.[1] Relaxin is secreted during the follicular and luteal phases, reaching its peak during the luteal phase.[5] Lastly, testosterone fluctuates throughout the cycle, and functions to contribute to the formation of estrogen.[6] Although the hormones that predominate during each phase are consistent among all women with normal functioning cycles, the levels of each hormone varies among individuals.[3]

The hormones controlling the menstrual cycle are thought to affect the overall integrity of the ACL by altering its structure.[7] In general, these hormones decrease the tensile properties of the ACL by binding to specific receptors on it.[7] Specifically estrogen, when bound to receptors on the ACL, has been shown to decrease fibroblast proliferation, subsequently decreasing collagen production.[7] This could theoretically result in a greater incidence of ACL injuries during the pre-ovulatory phase spanning days 1-14 of the menstrual cycle, when estrogen predominates. This theory has been supported by a case-control study in which female recreational skiers who sustained a non-contact ACL injury demonstrated a two-fold increase in injury rates during the pre-ovulatory phase compared to the uninjured controls.[8] However, other studies have reported contradictory results that refute the theory that hormonal variations during the menstrual cycle contribute to ligament laxity. For example, Van Luren et al[9] reported arthrometric analysis of ACL laxity that failed to demonstrate any variation in ACL laxity throughout the menstrual cycle. In addition, Belanger and colleagues[10] examined 18 female subjects and were unable to establish an association between increased ACL laxity and the menstrual phase.

The objective of this article is to review the literature regarding changes to anterior cruciate ligament laxity during the menstrual cycle, building on previous reviews by Zazulac et al[1] and Hewett et al[2]. A better understanding of the mechanism of injury may allow clinicians to identify females who are at greatest risk of ACL injury and subsequently contribute to injury prevention in female athletes.

Methods

A literature search was performed using the following electronic databases: Index to Chiropractic Literature, MEDLINE, CINAHL and Rehabilitation & Sports Medicine Source, through EBSCO Publishing. We combined controlled vocabulary terms with text words. In MEDLINE we exploded and searched the MeSH term menstrual cycle, which included fertile period, follicular phase, luteal phase and menstruation, and menstruation, and combined these terms with the MeSH term anterior cruciate ligament injury. Text words for these concepts included anterior cruciate ligament tear and anterior cruciate ligament injuries. This yielded 27 articles. Citations from specific articles (reference tracking) were then

Table 1:
Instrument Categories Used to Grade Articles for this Review

Grading Criteria:		
Baseline values of groups (/8)	No mention of baseline values	score 0;
	baseline values mentioned but not statistically significant	score 4;
	baseline values mentioned and not statistically significant	score 8.
Relevance of outcomes and clinical significance (/7)	No mention of outcomes and clinical significance	score 0;
	subjective outcome measures	score 3;
	objective outcome measures	score 5;
	both subjective and objective outcome measures	score 7.
Prognostic stratification (comorbidity and risk factors) (/6)	No clear mention of study inclusion or exclusion criteria	score 0;
	inadequate mention of inclusion or exclusion criteria	score 3;
	complete mention and description of inclusion and exclusion criteria	score 6.
Blinding strategies (/5)	No blinding strategies mentioned	score 0;
	single blinded study without method described and appropriate	score 2;
	single blinded study with method described and appropriate	score 3;
	double blinded study without method described and appropriate	score 4;
	double blinded study with method described and appropriate	score 5.
Contamination/ co-intervention (/4)	No mention of ways to control for contamination or co-intervention	score 0;
	some patients received some sort of contamination or co-intervention	score 2;
	assumed that no contamination or co-intervention took place due to immediate follow-up	score 3;
	contamination and co-intervention closely monitored and accounted for	score 4.
Compliance of subjects to study procedures (/4)	No mention or detail given to compliance of study subjects	score 0;
	compliance and co-intervention of patients monitored but not closely monitored	score 1;
	some patients were compliant and did not receive co-interventions and was closely monitored and detailed	score 2;
	compliance of subjects was assumed due to immediate follow-up	score 3;
	all patients were compliant and closely monitored and detailed	score 4.
Drop-out rates of subjects (/3)	No mention of drop-out rates	score 0;
	drop-out rates mentioned	score 1;
	no drop-out rates assumed due to immediate follow-up	score 2;
	number and reason for drop-outs described	score 3.
Publication date of research (/1)	Published prior to 2000	score 0;
	published after 2000	score 1.
Total Score: /38		

searched independently through selected databases followed by hand searching throughout the periodicals. Reference tracking yielded one article. Periodical searching yielded no eligible articles.

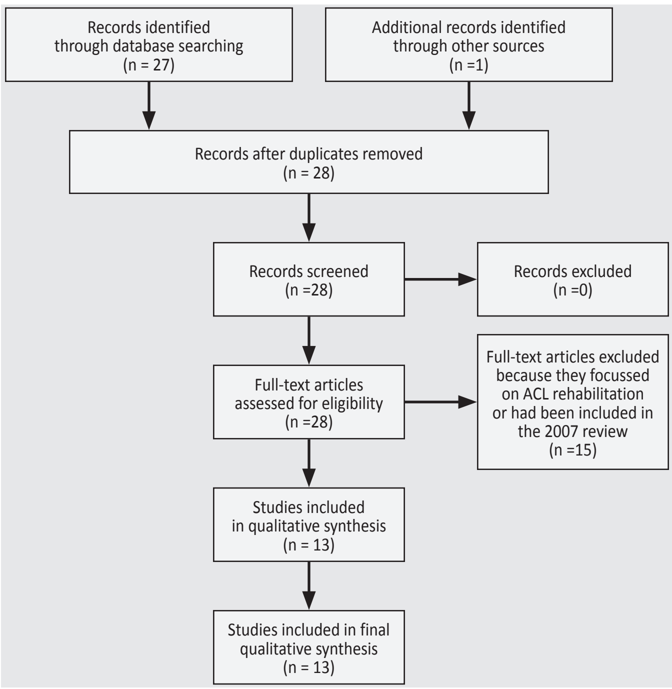
Inclusion/Exclusion Criteria

Inclusion criteria were as follows: female subjects of reproductive age; published between 1998 and August 2011; papers written in the English language and studies using human subjects only. Articles that focused on therapy for ACL injuries were excluded. Papers were also excluded if they had been reviewed in the most recent literature review by Hewett et al in 2007.[2] Using these inclusion/exclusion criteria 13 articles were selected for review.

Quality Appraisal

The methodological quality of the studies that met the selection criteria was assessed using a modified version of an instrument developed by Sackett (see Table 1).[11] Since the majority of research on the topic of ACL laxity and menstrual hormonal fluctuations is limited to observational study designs rather than randomized clinical trials,

Table 2:
Flow chart of retrieved articles used in this Review.



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

the 'assignment of patients' and 'follow-up levels' criteria were not included in our grading as they were deemed incompatible with the majority of the research designs. As a result, the instrument was modified and scored out of 38 rather than 50.

The eligible articles were randomly assigned to four authors (LB, DB, JC, SC). Each accepted article was reviewed by two authors independently. The data from all accepted articles were recorded onto a data extraction sheet by the authors as part of their review. The authors checked and edited all entries for accuracy and consistency. Recorded data included study authors and quality score, details of the study design, sample, interventions, outcome measures, and main results/conclusions of the study. Any discrepancies of scores between the authors were settled via discussion until consensus was reached.

Results

Thirteen articles met the inclusion criteria (see Table 2).[12-24] After methodological quality assessment of each article using the modified Sackett grading instrument, papers were allocated scores out of a possible 38 points (Table 3). Of the 13 articles, 9 articles investigated ACL injuries throughout the menstrual cycle and 4 articles investigated the issue of ACL laxity throughout the menstrual cycle

Table 3:

	Beynnon et al. 2006 AJSM	Eiling et al. 2007 KSSTA	Shultz et al. 2005 JOR	Park et al. 2009 AJSM 37(6)	Ruedl et al. 2009 KSSTA	Adachi et al. 2008 AOTS	Pollard et al. 2006 CB	Deie et al. 2002 IO	Hertel et al. 2006 KSSTA	Abt et al. 2007 KSSTA	Wojtys et al. 1998 AJSM	Park et al. 2009 AJSM	Park et al. 2008 BJSM
Baseline Values of Groups (/8)	8	8	4	8	8	4	4	8	4	4	4	4	4
Relevance of Outcomes & Clinical Significance (/7)	7	7	5	5	3	3	5	5	7	5	3	5	5
Prognostic Stratification (Comorbidity and Risk factors) (/6)	6	6	6	3	6	6	6	3	3	6	3	3	3
Blinding Strategies (/5)	0	3	3	0	0	0	0	0	0	0	0	0	0
Contamination/Co-Intervention (/4)	3	2	4	4	0	3	4	0	0	0	2	2	0
Compliance of Subjects to Study Procedures (/4)	3	0	1	1	3	3	0	0	1	0	3	0	0
Drop-out Rates of Subjects (/3)	2	0	1	1	2	2	0	3	3	3	2	0	0
Date of Publication (/1)	1	1	1	1	1	1	1	1	1	1	0	1	1
Total (/38)	30	27	25	23	23	22	20	20	19	19	17	15	13

- AJSM – American Journal of Sports Medicine
- KSSTA – Knee Surgery, Sports Traumology, Arthroscopy
- AOTS – Archives of Orthopaedic and Trauma Surgery
- BJSM – British Journal of Sports Medicine
- CB – Clinical Biomechanics
- IO – International Orthopaedics
- JOR – Journal of Orthopedic Research

(see Tables 4a and 4b respectively). Articles are listed in descending order of their score. In the event two or more articles had the same score, they were arranged alphabetically. A brief summary of each of the 13 articles graded in this study is provided in Table 4a and 4b.

The accepted studies, determined by Sackett et al, scored between 30 and 13 out of a possible 38 points on the Modified Sackett Score (MSS) instrument (Table 2,3). Eight[12-19] of the thirteen studies reported that knee ligament laxity changes throughout the menstrual cycle, although the phase during which this ligamentous laxity occurred varies throughout the cycle. Ruedl et al (MSS=23/39)[12], Adachi et al (MSS=22)[13], Wojtys et al (MSS=17)[14] and Park-b et al (MSS=13)[15] all reported increased knee laxity during the ovulatory phase and Beynnon et al (MSS=30)[16] reported increased knee laxity during the pre-ovulatory phase (compared to post-ovulatory phase). However, Schult et al (MSS=25)[17] and Deie et al (MSS=20)[18] reported increased knee laxity during the follicular phase and Parka (MSS=15)[19] reported increases knee laxity during the luteal phase of the menstrual cycle.

On the other hand, five studies[20-24] did not report any statistically significant changes in knee laxity during the menstrual cycle. Eiling et al (MSS=27)[20] reported that there was no statistically significant effect on anterior knee ligament laxity throughout the menstrual cycle and that 'musculoskeletal stiffness' was lower during the ovulatory phase of the menstrual cycle as compared to day one of menstruation and the mid-follicular phase. Two studies compared men to women with respect to knee laxity. The study by Deie et al[18] reported there was no statistical difference in the anterior knee movement of 8 men assessed during the same three week period as 16 women and the study by Pollard et al[21] that compared 12 men to 12 women reported that, while knee laxity increased following exercise, there was no difference across the sexes.

Discussions

Zazulak et al conducted a systematic review similar to ours in 2006.[1] Those researchers were able to retrieve nine studies. Subjects included collegiate athletes, high-school athletes, recreational athletes, non-athletes and 'unspecified' sport participants. Cohort sizes ranged from 7 to 41. Anterior tibiofemoral movement was measured in all studies using KT 1000 or KT 2000 arthrometers.[1]

In that review, six of the nine reviewed studies reported no statistically significant effect of the menstrual cycle on ACL laxity. However, the reviewers reminded the reader that the majority of these six studies based their observations on a single sampled day of the cycle, or randomly sampled across the cycle without hormonal or cycle landmark confirmation.[1] Of the three studies that did report increased laxity of ACL during the menstrual cycle, all three reported it occurred during the ovulatory or post-ovulatory (luteal) phase[1], a finding similar to what we found among the 13 articles we reviewed. Despite diversity in the literature, Zazulak et al[1] suggested that the three studies which found a positive association between the menstrual cycle and ligament laxity were superior in study design, methodology and consistency compared to the 6 studies which failed to show any association, thereby concluding that the menstrual cycle may have a significant effect on anterior knee laxity.

Hewett et al[2] performed a similar systematic review to the one by Zazulak et al[1], with the primary difference being that Hewett et al reviewed articles that investigated the effects of the menstrual cycle on anterior cruciate ligament injury risk among high-risk female athletes, whereas Zazulek et al investigated the effect of the menstrual cycle on anterior knee laxity. In the Hewett et al[2] review, seven studies met the study's inclusion criteria. Hewett et al[2] reported that all seven articles favoured an effect of the first half of the menstrual cycle for the increased ACL injuries, most commonly during the pre-ovulatory phase. These authors also reported that the use of oral contraceptives in combination with neuromuscular training may increase the stability of the knee joint and decrease the risk of injury to female athletes.[2] Hewett et al suggested that disproportionate or isolated quadriceps recruitment can create forces higher than those required for ACL failure.[3] Therefore, neuromuscular training should focus on balancing hamstrings-to-quadriceps strength and recruitment in order to increase stability of the knee.

While Zazulak et al[2] focused on knee laxity and Hewett et al[1] focused on injury, this most recent review looked at a combination of both laxity and injury. The results of our review are in agreeance with Zazulak et al[2] and Hewett et al[1], supporting an effect of menstrual cycle on anterior cruciate ligament laxity. While the association between ligament laxity and hormonal fluctuations during the menstrual cycle has been suggested, there remains discrepancy concerning which phase of the menstrual cycle

Table 4a:
Studies Investigating ACL Laxity

Reference	Objective	Study Design	Score /38	Patients/Conditions	Methods	Main Outcome Measures	Main Results/Conclusions
Eiling et al 2007	1. To examine changes in lower limb musculo-tendinous stiffness (MTS) over the course of the menstrual cycle 2. Investigate the interaction of warm-up on MTS	Cross-sectional Study	27	11 adolescent females. Played netball for minimum 5 yrs. • eight A-grade players and state representatives • two B-grade players and two C-grade players The average age, height and weight of the subjects was: • 16.3 ± 0.65 years • 164.12 ± 6.2 cm and 60.72 ± 6.3 kg Trained min 2 hrs per week. Consistent menstrual cycles for 3 mths. Menarche >1 yr ago. No use of contraceptives or other hormones for 3 mths. No history of serious lower limb injury. Normal joint ROM.	Subjects documented menstrual history for 3 months prior and post testing, Each subject tested at each of the 4 phases of the cycle: – blood levels for LH, FSH, estradiol and progesterone. – ACL laxity using KT-2000. – MTS assessed before and after 5 min cycling warm up using unilateral hopping on force plate.	1. Blood levels LH, FSH, estradiol and progesterone. • The levels were analysed which allowed the levels to be matched with the testing date • If the values of the hormone analysis were not within the documented ranges for the specific phase, it was assumed that either the test date was miscalculated or that the cycle was anovulatory • In both cases, the subject was re-tested for that particular phase in the subsequent cycle. 2. KT-2000 • The knee was placed in 30 deg. of flexion as the subject lay supine on a bench 3. Force plate • Following a warm-up of 5 min of cycling at 50 W together with ten run-ups and netball landings subjects were instructed to perform a unilateral hop on a force plate in time with a metronome at a frequency of 2.2 Hz	No statistically significant effect of the menstrual cycle on anterior knee laxity. MTS significantly decreased following warm up. • Repeated measures ANOVA revealed significant ($P < 0.05$) main effects of test-session and warm-up on MTS for the dominant leg. • MTS was found to significantly decrease by 4.2% following the warm-up intervention It was significantly lower during the ovulatory phase compared to day one of menstruation and mid-follicular phase, 8.7 and 4.5%.
Schultz et al 2005	To investigate if hormone levels across the menstrual cycle can affect anterior knee laxity	Cross-sectional study	25	22 females with normal self-reported menstrual history in the previous 6 months Between the ages of 18 and 30, with a body mass index (BMI = weight/height2) less than or equal to 30 **Inclusion:** • no history of pregnancy • no use of oral contraceptives or other hormone-stimulating medications for 6 months • non-smoking behavior • two healthy knees with no prior history of joint injury or surgery, no medical conditions affecting the connective tissue • physical activity limited to 7 h or less per week. **Exclusion:** • experienced an anovulatory cycle or missed three or more consecutive days of testing	Measured blood levels of estradiol, progesterone and testosterone. Then measured knee joint laxity with an arthrometer	Minimum and peak levels of blood estradiol, progesterone, and testosterone. Knee laxity using an arthrometer	The minimum concentrations of estradiol and progesterone in the early follicular phase are important factors in determining sensitivity of the knee joint's response to changing hormone levels. When minimum progesterone concentrations were higher and minimum estradiol concentrations were lower during the early follicular phase, females experienced greater increases in knee laxity across the menstrual cycle with attainment of peak estradiol and testosterone levels post ovulation.
Park et al 2009 (Alterations in knee joint...)	To investigate whether the hormonal cycle has an influence on knee joint mechanism and whether increased knee joint loading during the menstrual cycle affects knee joint mechanics.	Controlled laboratory study.	23	26 healthy women: • age 22.7 ± 3.3 years • height, 170.1 ± 7.1 cm • mass, 65.0 ± 9.3 kg • body mass index (BMI), 22.4 ± 2.5 • average menstrual cycle, 28.9 ± 2.7 days • activity level, 8.7 ± 4.4 h/wk **Inclusion:** • required that the subject have a normal menstrual cycle • no history of oral contraceptive use, and no previous knee injury Refrain from exercise 6 hrs prior to testing.	Blood samples drawn at 3 different phases of the menstrual cycle in each subject. Knee joint loading was then measured during each phase using the KT-2000 arthrometer. Motion analysis testing of the knee was then performed.	Blood serum estradiol and progesterone. KT-2000	No significant difference in knee joint mechanics between phases. However, increased knee joint laxity was associated with higher knee joint loads during movements.

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Table 4a:
Studies Investigating ACL Laxity (continued)

Reference	Objective	Study Design	Score /38	Patients/Conditions	Methods	Main Outcome Measures	Main Results/Conclusions
Pollard et al 2006	To investigate the collective effects of gender, estrogen and exercise on anterior knee laxity in active individuals	Observational Study	20	12 women: age 24.8 years 12 men: age 24.3 years – All 24 men and women had a history of participating in high school and/or recreational cutting and landing sports which included basketball, volleyball, field hockey and soccer. – **Inclusion criteria:** subjects had to have performed moderate exercise at least 4 times a week for at least 45 mins in duration for 2 months prior to participation in the study, had to have no history of significant lower extremity injury, were injury-free at the time of data collection, females had to have not taken oral contraceptives for the past 6 months and had experienced a normal 27-31 day cycle for the past 3 months. – **Exclusion:** if they had participated in collegiate level athletics at any time	All subjects came to the lab prior to data collection for a pre-collection session to familiarize them with the KT-1000. Female subjects were given ovulation kits that detect the surge of LH immediately preceding ovulation to determine the time of ovulation. Each completed an informed consent and was instructed to refrain from exercise prior to data collection on that day. Females assigned to start data collection at the onset of menses or the onset of ovulation and completed 5 day data collections following the same protocol each which occurred at a specific time to correlate with different phases of the menstrual cycle – onset menses, 10 and 12 days post onset, 7 and 9 days post ovulation. Male subjects started collection on a day of convenience and completed 3 data collections following the same protocol as females, 10-12 days apart	Exercise: • Subjects ran on a treadmill for 15 min at a self-selected pace. • The subject was asked to set the pace to correspond to what they would consider ''moderately hard''. Once this pace was established, it was used throughout the rest of the data collections. • For each subsequent treadmill run, the subject was instructed to warm up during the first three minutes and to reach the predetermined pace by the end of 3 min. • immediately following the treadmill run, subjects were instructed to perform three dynamic lower extremity tasks consisting of the following: two minutes of weaving (grapevine) along a 20 m long runway; two minutes of left and right cutting along 2 m wide runway; and, 25 jump downs from a 46 cm step. KT-1000 arthrometer. Blood samples: looking at estrogen levels across the menstrual cycles	Knee laxity increased following exercise but did not differ across genders.
Deie et al 2002	To determine whether ACL laxity in women changes significantly during their menstrual cycles	Case-Control study.	20	16 women, aged 21-23 (average age of 21.6 years) 8 men No BCP Regular menses (28±4 days) No previous knee injury	Measurements of their knees using KT-2000 arthrometer were performed 2-3 times every week over 4 consecutive weeks. Women measured their basal body temp daily for 4 weeks and estradiol and progesterone levels in their blood weekly. From their BBT or estradiol and progesterone levels the follicular, ovulatory, and luteal phases were delineated. 342 measurements were made. 158 measurements= follicular phase, 56=ovulatory, 128=luteal phase – Men's measurements of their knees using KT-2000 were performed 3 times a week over a 3 week period. 144 measurements were taken with 48 measurements in each of the first, second and third phases (based on when the measurement was taken in what week)	Arthrometer Basal body temp Blood samples	In men, no statistical significance with anterior movement through the 3 week period. In women, anterior or terminal stiffness was higher in the follicular phase than the ovulatory phase, which was in turn higher than the luteal phase.
Hertel et al 2006	To investigate changes in neuromuscular control and laxity at the knee across the menstrual cycle	Cross-sectional study.	19	– 14 female collegiate athletes • age 19.3 ± 1.3 years • height 163.6 ± 8.5 cm • mass 59.4 ± 6.8 kg. – normal ovulatory menstrual cycles (28-35 day cycles) with confirmed ovulation – not taking oral contraceptives – no history of serious knee injury – Subjects participated in either competitive soccer or stunt cheerleading	Urine hormone levels and ovulation measured. Neuromuscular performance and laxity of knee were measured in each phase of the cycle.	Hormone levels. Peak flexion and extension torque. Hamstring: quadriceps strength. Joint position sense. Centre of pressure velocity. Anterior knee laxity.	Neuromuscular control and knee joint laxity do not change substantially across the menstrual cycle despite varying estrogen and progesterone levels.

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Table 4a:
Studies Investigating ACL Laxity (continued)

Reference	Objective	Study Design	Score /38	Patients/Conditions	Methods	Main Outcome Measures	Main Results/Conclusions
Abt et al 2007	To determine if changes in the levels of estradiol and progesterone significantly alter fine motor coordination, postural stability knee strength and knee joint kinematics and kinetics between the menses, post-ovulatory, and mid-luteal phases of the menstrual cycle.	Cross-sectional study.	19	10 physically active females were recruited from the local university • Age: 21.4 ± 1.4 years • Height: 1.67 ± 0.06 m • Mass: 59.9 ± 7.4 kg who do not use oral contraceptives. – subjects were screened for: • history of injury • nutritional practices • menstrual dysfunction • thyroid dysfunction, and physical activity. **Exclusion:** • mid-luteal progesterone level less than 10 ng/ml • history of serious knee injury or other lower extremity injury within the prior 6 months • previous or current eating disorder • previous or current menstrual dysfunction	Measured single leg postural stability, fine motor coordination, knee strength, knee biomechanics, and serum estradiol and progesterone.	Estradiol Progesterone Fine motor coordination Postural stability Hamstring: quad strength Knee flexion and valgus excursion Peak proximal ant tibial shear force Flexion and valgus moments at peak proximal ant tibial shear force	Neuromuscular and biomechanical characteristics are not influenced by estradiol and progesterone fluctuations
Park et al 2009	To determine whether changing hormone levels influence joint laxity and stiffness of a non-contractile knee joint and knee joint structures using a new analysis technique. To determine whether subsets of women exist who demonstrate or do not demonstrate changes in knee laxity in response to circulating hormone levels throughout their menstrual cycle.	Observational Study	15	26 women • age, 22.7 ± 3.3 years • height, 170.1 ± 7.1 cm • mass, 65.0 ± 9.3 kg • body mass index (BMI), 22.4 ± 2.5 • average menstrual cycle, 28.9 ± 2.7 days • and activity level, 8.7 ± 4.4 h/wk. • Most subjects regularly participated in a sports activity at a recreational level. **Inclusion:** • no previous knee injuries • never been pregnant • have regular menstrual cycles (approximately 28 days) with no missed cycles over the previous 24 months • no oral contraceptive use for the previous 6 months	Each completed a blood draw and laxity tests at 3 different times during her menstrual cycle. Blood samples were collected to determine the levels of estradiol and progesterone, indicating an appropriate phase of testing. Passive laxity and stiffness were measured using arthrometer	Self reported menstrual history Arthrometer Measured for estradiol and progesterone	Lowest hormones in follicular phase, highest in luteal phase Lowest estradiol and progesterone were in follicular and highest were in luteal phase – Greater knee laxity at 89N was recorded in ovulation compared to luteal phase – Max knee laxity during ovulation significantly exceeded max laxity during follicular phase
Park et al 2009 (Relationship between...)	To investigate whether changing knee laxity during the menstrual cycle correlates with changing knee joint loads in a cutting maneuver	Cross-sectional study	13	25 healthy women: • mean age 22.7 years • height 170.2 cm • mass 64.7 kg • body mass index 22.3 menstrual cycle 28.9 days • activity levels 8.7 h/week The subjects regularly participated in sports activity at a recreational level. **Inclusion:** • a normal menstrual cycle • no history of oral contraceptive use • no knee injury within the preceding 6 months	Serum hormone concentrations were assessed and knee joint laxity was measured during the follicular, ovulation and luteal phases. Performed 10 trials of a cutting maneuver.	Knee joint laxity Peak knee angle Knee joint moment Knee joint impulse Blood hormone levels	Increased knee laxity was observed during ovulation compared with the luteal phase, but no significant changes in knee mechanics corresponding to menstrual phases were found.

Table 4b:
Studies Investigating ACL Injury

Reference	Objective	Study Design	Score /38	Patients/Conditions	Methods	Main Outcome Measures	Main Results/Conclusions
Beynnon et al 2006	To determine the relationship between the menstrual cycle and ACL injury	Case-control study	30	200 subjects, female only	Direct measurement of blood concentrations of progesterone and estradiol at time of injury. Self reported menstrual history.	Serum levels of progesterone and estradiol. Menstrual history.	The risk of sustaining an ACL tear increases during the pre-ovulatory phase of the menstrual cycle as compared to the post-ovulatory phase (3x)
Ruedl et al 2009	1. investigate a possible protective effect of oral contraceptive use against ACL injuries in rec. skiers 2. compare the frequencies of non-contact ACL injuries in the preovulatory phase with that in the postovulatory phase	Case-control Study	23	93 females With non-contact ACL injuries 93 female recreational skiers with a non-contact ACL injury and 93 age matched controls	MRI was used to diagnose ACL injury. Only non-contact ACL injuries were included. On and off pill users were included. Female recreational alpine skiers are treated in a ski clinic, which is located in close proximity to the ski resort.	Questionnaire, with information on: • Age • Height • Weight • Previous knee injuries of either leg A second questionnaire developed and validated by Wojtys et al. was used: • age at the start of menstruation • date of last menstruation • average length of menstruation • the use of oral contraceptives	ACL injury is greater in the pre-ovulatory phase. Use of oral contraceptives and previous knee injuries showed no association with ACL injury rate.
Adachi et al 2008	To determine if non-contact ACL injuries occurred randomly or correlate with a specific phase of the menstrual cycle in teenaged female athletes	Case-control Study	22	18 females aged 11-18 ACL injury (non-contact) confirmed by MRI. No history of pregnancy. No use of oral contraceptives or hormone stimulating meds. Consistent menstrual cycle last 6 months. Competitive or recreational athlete.	Subjects completed a questionnaire that documented injury history, menstrual history and activity level at each phase of the cycle to determine in which phase their injury occurred.	Questionnaire: • injury history • menstrual history • subjective activity levels on each phase of the menstrual cycle A second questionnaire developed by Wojtys et al. was used to document: • age • height • weight • detailed history of the menstrual cycle (including frequency and regularity, date of last menstrual period, average length of cycle, premenstrual and menstrual symptoms, and oral contraceptives)	Significant statistical association was found between the phase of the menstrual cycle and time of ACL injuries. More injuries occurred during the ovulation phase (72%). Few injuries in luteal and follicular phases.
Wojtys et al 1998	To investigate the variation in ACL injury rates during the female monthly cycle	Observational Study	17	28 women with ACL tears in the last 3 months.	Women with a history of either irregular or missed menstrual cycles were excluded and only patients with noncontact ACL injuries were included. – 28 met these criteria and were asked to fill out a questionnaire and provide their age, height, weight, level and freq. of sports participation, and previous knee injuries. Asked to document the date and mechanism of acute ACL injury, including the number of minutes played before the injury occurred, whether the injury occurred during a practice or game and the nature of the ACL injury. Each woman was asked to provide a detailed history of her menstrual cycle, frequency and regularity, date of last period and average length, premenstrual symptoms and oral contraceptive or hormone replacement use.	Questionnaire: • age • height • weight • level and frequency of sports participation • previous knee injuries • date and mechanism of the acute ACL injury (including the number of minutes played before the injury occurred, whether the injury occurred during a practice or game situation, and the nature of the ACL injury • history of menstrual cycle (frequency, regularity, date of last menstrual period, average length of cycle, premenstrual symptoms, and oral contraceptive use	The association between the ovulatory phase and the rate of ACL injury is statistically significant. Further information needed.

is associated with greater ligament laxity. The current review found that the majority of studies (4 studies out of 8) that reported a positive association between increased laxity, injury and the menstrual cycle implicated the ovulatory phase as the most significant time for laxity to occur. These findings are somewhat in concordance with the conclusions of Zazulak et al[2], who identified the greatest laxity during the ovulatory and post-ovulatory phases. In contrast, Hewett et al[1] identified that the greatest injury risk occurred during the pre-ovulatory phase.

Overall, limited evidence from the three reviews supports the theory that ACL ligament laxity varies with the fluctuations of the hormonal cycle, thus predisposing female athletes to ACL injury. What remains to be clarified is what phase of the cycle females are most at risk. Future research should aim to clarify whether this fluctuation in ligament laxity is consistent amongst all women with hormonal fluctuations throughout their cycle, or whether ligament laxity is dependent on the absolute or relative hormonal level changes throughout a woman's cycle. Future studies can address this issue by focusing more stringently on measuring hormone levels and by examining women over a longer period of time (more than one cycle) to try and establish whether a trend in hormonal levels and ligament laxity can be established and a phase of increased risk identified.

Limitations

Many limitations were encountered throughout the review of the recent literature. Limitations included: the majority of the research was conducted during only one menstrual cycle per participant, which does not account for variation from cycle to cycle; there was no standardized definition of the phases of the menstrual cycle, resulting in variation of the phases from paper to paper; typically only one knee was assessed per participant and therefore the results cannot be confidently distinguished from conditions that may have been pre-existent in that knee; the majority of studies were conducted exclusively on women with normal 28-day cycles and; women who were on oral contraceptives were often excluded by design. The average woman, and the elite athlete, are not so easily categorized- especially since menstruation may cease among some high performance athletes with low body mass indexes, and thus the results reported in these studies may not be extrapolated to the female population most at-risk of ACL injury.

Other limitations of this review are that we only searched for articles in English and did not go further back than 1998, since that was where other similar reviewers ended. Another limitation was our use of an adapted Sacket instrument for the purposes of this review. Although it had face validity to do so, to the best of our knowledge there is no evidence that specifically supports the validity of the modifications we made to Sackett's original instrument. Furthermore, this tool does not assess important aspects including confounding factors, participation rates, study population consistency or selection bias. Lastly, 5 of the 13 studies accepted in this review are cross-sectional and therefore cannot be used to determine any cause and effect relationship between menstrual cycle and knee ligament laxity.

Conclusions

There is preliminary evidence to suggest that ligamentous laxity of the knee changes throughout the course of a women's menstrual cycle, with the majority of studies reporting the greatest change is during the ovulatory phase. However it is important to note that the evidence remains inconsistent and is based predominantly on studies of low methodological quality. Certainly better clinical trials need to be conducted that follow women over several menstrual cycles and that include women not on a standard 28-day cycle. Moreover, clinical trials investigating changes to ACL laxity should assess both knees. That said, this review, as well as the previously published study by Hewitt et al[2,3], suggest that healthcare professionals caution their female patients that injury may occur during different phases of their menstrual cycle- particularly the ovulatory phase. It may be prudent for female athletes to take the necessary precautions when exercising vigorously during certain stages of their menstrual cycle. Since it does appear that at least some women may experience ligament laxity during different phases of their menstrual cycle, patients can be encouraged to diarize any injuries they may sustain and monitor if they typically occur during a particular phase of their menstrual cycle. In addition, due to the lack of consensus on the phase at which increased laxity and injury occurs, healthcare professionals can provide greater benefit than a warning of the possibility of increased laxity with the implementation of a training program that focuses on balancing lower limb musculature strength as a preventative measure.

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