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 correspondaient 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, correspondaient 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. 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. 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. 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). An additional theory posits increased ligament laxity is related to hormonal fluctuations during the menstrual cycle.

The menstrual cycle is controlled by the pituitary-hypothalamic-ovarian axis and involves the complex interaction of estrogen, progesterone, relaxin and testosterone. 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. The cycle ends with the luteal phase extending from days 15-28 during which time progesterone levels surpass that of estrogen levels. Relaxin is secreted during the follicular and luteal phases, reaching its peak during the luteal phase. Lastly, testosterone fluctuates throughout the cycle, and functions to contribute to the formation of estrogen. 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.

The hormones controlling the menstrual cycle are thought to affect the overall integrity of the ACL by altering its structure. In general, these hormones decrease the tensile properties of the ACL by binding to specific receptors on it. Specifically estrogen, when bound to receptors on the ACL, has been shown to decrease fibroblast proliferation, subsequently decreasing collagen production. 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. 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. reported arthrometric analysis of ACL laxity that failed to demonstrate any variation in ACL laxity throughout the menstrual cycle. In addition, Belanger and colleagues 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 and Hewett et al. 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
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. 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). 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,
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 2:
**Flow chart of retrieved articles used in this Review.**

<table>
<thead>
<tr>
<th>Records identified through database searching (n = 27)</th>
<th>Additional records identified through other sources (n = 1)</th>
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<tr>
<td>Records after duplicates removed (n = 28)</td>
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<td>Records screened (n = 28)</td>
<td>Records excluded (n = 0)</td>
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<tr>
<td>Full-text articles assessed for eligibility (n = 28)</td>
<td>Full-text articles excluded because they focused on ACL rehabilitation or had been included in the 2007 review (n = 15)</td>
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<tr>
<td>Studies included in qualitative synthesis (n = 13)</td>
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<td>Studies included in final qualitative synthesis (n = 13)</td>
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</table>


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<td>Relevance of Outcomes &amp; Clinical Significance (77)</td>
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<tr>
<td>Blinding Strategies (5)</td>
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<td>Contamination/Co-Intervention (4)</td>
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<td>Compliance of Subjects to Study Procedures (4)</td>
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<tr>
<td>Drop-out Rates of Subjects (3)</td>
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<td>Date of Publication (1)</td>
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<td>1</td>
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<td>Total (/38)</td>
<td>30</td>
<td>27</td>
<td>25</td>
<td>23</td>
<td>23</td>
<td>22</td>
<td>20</td>
<td>19</td>
<td>19</td>
<td>17</td>
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</tbody>
</table>

- **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
In that review, six of the nine reviewed studies re-
ported 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) phase1, a finding similar to what
we found among the 13 articles we reviewed. Despite di-
versity in the literature, Zazulak et al1 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, there-
by concluding that the menstrual cycle may have a signifi-
cant effect on anterior knee laxity.

Hewett et al2 performed a similar systematic review to
the one by Zazulak et al1, with the primary difference be-
ing that Hewett et al reviewed articles that investigated
the effects of the menstrual cycle on anterior cruciate liga-
ment injury risk among high-risk female athletes, whereas
Zazulak et al investigated the effect of the menstrual
cycle on anterior knee laxity. In the Hewett et al2 review,
seven studies met the study’s inclusion criteria. Hewett
et al2 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 contracep-
tives in combination with neuromuscular training may in-
crease 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 bal-
ancing hamstrings-to-quadriceps strength and recruitment
in order to increase stability of the knee.

While Zazulak et al1 focused on knee laxity and Hewett
et al1 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 al2 and Hewett
et al1, 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 dis-
crepancy concerning which phase of the menstrual cycle

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 re-
**Objective**
22 females with normal self-tendinous stiffness (MTS) over the course of the menstrual cycle.

**Methods**
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.
- MTS assessed before and after 5 min cycling warm up using unilateral hopping on force plate.

**Main Results/Conclusions**
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%.

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### Table 4a:
Studies Investigating ACL Laxity

<table>
<thead>
<tr>
<th>Reference</th>
<th>Objective</th>
<th>Study Design</th>
<th>Score</th>
<th>Patients/Conditions</th>
<th>Methods</th>
<th>Main Outcome Measures</th>
<th>Main Results/Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eiling et al 2007</td>
<td>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.</td>
<td>Cross-sectional Study</td>
<td>27</td>
<td>31 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 &gt; 1 yr ago. No use of contraceptives or other hormones for 3 mths. No history of serious lower limb injury. Normal joint ROM.</td>
<td>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.</td>
<td>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</td>
<td>No statistically significant effect of the menstrual cycle on anterior knee laxity. MTS significantly decreased following warm up. • Repeated measures ANOVA revealed significant (P &lt; 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%.</td>
</tr>
<tr>
<td>Schultz et al 2005</td>
<td>To investigate if hormone levels across the menstrual cycle can affect anterior knee laxity.</td>
<td>Cross-sectional study</td>
<td>25</td>
<td>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/height^2 &lt; 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 hr per week. Exclusion: • experienced an anovulatory cycle or missed three or more consecutive days of testing.</td>
<td>Measured blood levels of estradiol, progesterone and testosterone. Then measured knee joint laxity with an arthrometer.</td>
<td>Minimum and peak levels of blood estradiol, progesterone, and testosterone. Knee laxity using an arthrometer.</td>
<td>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.</td>
</tr>
<tr>
<td>Park et al 2009</td>
<td>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.</td>
<td>Controlled laboratory study</td>
<td>23</td>
<td>26 healthy women: • age 22.7 ± 1.3 years • height, 170.1 ± 7.1 cm • mass, 65.0 ± 5.3 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.</td>
<td>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.</td>
<td>Blood serum estradiol and progesterone. KT-2000</td>
<td>No significant difference in knee joint mechanics between phases. However, increased knee joint laxity was associated with higher knee joint loads during movements.</td>
</tr>
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</table>
### Table 4a: Studies Investigating ACL Laxity (continued)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Objective</th>
<th>Study Design</th>
<th>Score /38</th>
<th>Patients/Conditions</th>
<th>Methods</th>
<th>Main Outcome Measures</th>
<th>Main Results/Conclusions</th>
</tr>
</thead>
</table>
| 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                                 | 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)

<table>
<thead>
<tr>
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</table>
| 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 menstrual, 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 | Neurovascular 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, 1.70 ± 0.1 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, 1.70 ± 0.2 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. |
Anterior cruciate ligament laxity related to the menstrual cycle: an updated systematic review of the literature

Table 4b: Studies Investigating ACL Injury

<table>
<thead>
<tr>
<th>Reference</th>
<th>Objective</th>
<th>Study Design</th>
<th>Score</th>
<th>Patients/Conditions</th>
<th>Methods</th>
<th>Main Outcome Measures</th>
<th>Main Results/Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beynnon et al 2006</td>
<td>To determine the relationship between the menstrual cycle and ACL injury</td>
<td>Case-control study</td>
<td>30</td>
<td>200 subjects, female only</td>
<td>Direct measurement of blood concentrations of progesterone and estradiol at time of injury. Self reported menstrual history.</td>
<td>Serum levels of progesterone and estradiol. Menstrual history.</td>
<td>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).</td>
</tr>
<tr>
<td>Ruedl et al 2009</td>
<td>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</td>
<td>Case-control Study</td>
<td>23</td>
<td>93 females With non-contact ACL injuries and 93 age matched controls</td>
<td>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.</td>
<td>Questionnaire, with information on: Age, Height, Weight, Previous knee injuries of either leg</td>
<td>ACL injury is greater in the pre-ovulatory phase. Use of oral contraceptives and previous knee injuries showed no association with ACL injury rate.</td>
</tr>
<tr>
<td>Adachi et al 2008</td>
<td>To determine if non-contact ACL injuries occurred randomly or correlate with a specific phase of the menstrual cycle in teenaged female athletes</td>
<td>Case-control Study</td>
<td>22</td>
<td>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.</td>
<td>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)</td>
<td>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.</td>
<td></td>
</tr>
<tr>
<td>Wojtys et al 1998</td>
<td>To investigate the variation in ACL injury rates during the female monthly cycle</td>
<td>Observational Study</td>
<td>17</td>
<td>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.</td>
<td>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</td>
<td>The association between the ovulatory phase and the rate of ACL injury is statistically significant. Further information needed.</td>
<td></td>
</tr>
</tbody>
</table>
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. Further 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\(^2\), 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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References


