

Review

The Influence of the Menstrual Cycle and Oral Contraceptives on Knee Laxity or Anterior Cruciate Ligament Injury Risk: A Systematic Review

Juliette Moriceau ¹, Amandine Fevre ¹, Diego Domínguez-Balmaseda ^{1,2} , Ángel González-de-la-Flor ¹ ,
Julia Simón-Arecas ¹ and Guillermo García-Pérez-de-Sevilla ^{1,*} 

¹ Faculty of Sport Sciences, Department of Physiotherapy, Universidad Europea de Madrid, 28223 Madrid, Spain

² Masmicrobiota Group, Faculty of Health Sciences, Universidad Europea de Madrid, 28223 Madrid, Spain

* Correspondence: guillermo.garcia@universidadeuropea.es

Abstract: Women are two to four times more prone to anterior cruciate ligament (ACL) injuries than men. This raises questions about the role of the hormonal cycle in knee laxity, which may lead to increased tibial displacement and thus ACL tears. The objective was to update scientific knowledge on the influence of the menstrual cycle on knee laxity and the risk of ACL injury, with a focus on anterior tibial displacement, and on hormonal levels influenced or not by oral contraceptive use. Observational studies obtained from Pubmed, Web of Sciences and Scopus and published between 2015 and 2022 were included in this review. Studies were required to include data on menstrual cycle with/without oral contraceptives (OC) and knee laxity and/or ACL injury. A total of ten studies were selected for this systematic review. Three studies about hormone concentration and knee laxity showed an increase in estradiol during the ovulatory phase compared to the follicular phase. Of the five studies on OC, four showed a decrease in ACL laxity. Finally, four studies assessed ACL injury. The menstrual cycle appears to influence knee laxity in women. An increase in certain hormone levels was observed in the ovulatory and luteal phases when the anterior tibial translation was greater in the knee. However, based on the literature, we cannot conclude that there is a correlation between the menstrual cycle and the risk of ACL injury.

Keywords: anterior cruciate ligament; menstrual cycle; women; knee



Citation: Moriceau, J.; Fevre, A.; Domínguez-Balmaseda, D.; González-de-la-Flor, Á.; Simón-Arecas, J.; García-Pérez-de-Sevilla, G. The Influence of the Menstrual Cycle and Oral Contraceptives on Knee Laxity or Anterior Cruciate Ligament Injury Risk: A Systematic Review. *Appl. Sci.* **2022**, *12*, 12627. <https://doi.org/10.3390/app122412627>

Academic Editors: Massimo Ralli, Gaspare Palaia and Alice Bruscolini

Received: 8 November 2022

Accepted: 7 December 2022

Published: 9 December 2022

Publisher's Note: MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.



Copyright: © 2022 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

1. Introduction

The professionalization of women's sports, especially football, considerably raised the demand for physical training in recent years [1,2], leading to an increase in injuries [3–5]. Epidemiological data indicate that women have a two to four times higher risk of anterior cruciate ligament (ACL) tears than men [6]. This percentage can be increased up to eight times in female athletes [7–9]. Since ACL injuries have a considerable impact on quality of life and medical costs, it is relevant to determine the injury risk caused by the difference in knee laxity according to the phases of the menstrual cycle. For this reason, knowledge of the correlation between physiological variation in women during the menstrual cycle and the risk of injury should be a key issue in the 21st century [10].

The menstrual cycle is defined as a period designating “physiological changes that occur in fertile women and other female primates for the purpose of sexual reproduction” [11]. In women, the menstrual cycle has an average duration of 28 days. During this period, hormonal fluctuations are present and make it possible to differentiate four phases: pre-ovulatory, ovulatory, post-ovulatory and menstrual. These episodes are controlled by several hormones, ovarian and steroidal, which each have different actions. During the pre-ovulatory or follicular phase, there is an increase in estrogen and follicle-stimulating hormone (FSH) levels [12]. Ovulation, on the other hand, is caused by a spike in luteinizing

hormone (LH) in synergy with a spike in FSH, produced by an increase in estrogen. Successively, the post-ovulatory or luteal phase is characterized by an increase in the concentration of progesterone and inhibition of FSH and LH [13].

The menstrual cycle can be regulated by taking exogenous hormones, for medical reasons or as a contraceptive method. For these reasons, the use of oral contraceptives (OC) is increasingly common among young women. To date, no consensus could be reached on the positive or negative effect of OC on the incidence of ACL injuries [14].

Knee laxity is characterized by the anterior displacement of the tibia on the femur when a load is applied to the posterior surface of the tibia. The main stabilizer of the knee, limiting this movement, is the ACL [13]. During excessive anterior translations, this ligament is put under tension, and can therefore be subject to ruptures. Many studies have reported greater anterior laxity at the knee in women compared to men, which may lead to a greater risk of ACL injury [15–17], especially with the onset of puberty [18]. Therefore, hormonal fluctuations in women must be taken into consideration. Indeed, steroid hormones influence ligament metabolism, as demonstrated by Liu et al. on the ACL [19]. The estrogens and progesterone exert an action on the synthesis of collagen, modifying the fibroblastic property and therefore its mechanical resistance to tension. In fact, correlations between increased blood estrogen concentration and reduced collagen levels have been observed, due to a decrease in the number of fibroblasts in the ACL [20]. Studies show that a high level of estradiol is responsible for the decrease in fibroblast proliferation and therefore the synthesis of ligament collagen [19,21,22], which affects ligament resistance, increasing its elasticity and its vulnerability to injury. Looking at the composition of the ACL, Faryniarz et al. have identified receptors for relaxin, a hormone known for its elastic property in tissues [23]. These findings suggest an action of this hormone on ACL laxity, which is predominant in women [23].

Previously, two systematic reviews have been conducted to determine the association between ACL tears, knee laxity and menstrual cycle [6,24]. However, more recent data have been published since their research. Therefore, the objective of this systematic review is to update the scientific knowledge about the influence of the menstrual cycle and OC on knee laxity and ACL injuries.

2. Methods

2.1. Study Design

A systematic review was performed following the recommendations of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020 criteria). This review was registered in PROSPERO with the code number CRD42022345257.

2.2. Data Source

The searches were performed by two independent investigators in the PubMed, Scopus and Web of Sciences databased. A search equation using MESH terms was defined to obtain a precise search: (“menstrual cycle” OR “oral contraceptive” OR “hormones”) AND (“knee laxity” OR “Anterior Cruciate Ligament injuries” OR “Anterior Cruciate Ligament laxness”).

2.3. Inclusion/Exclusion Criteria

A publication date filter was added from 2015 to July 2022 to update the scientific knowledge, since the studies of the last systematic review on this subject (6) dated from 2015. After duplicates were removed, studies were excluded if they did not match the following inclusion and exclusion criteria: (i) article written in English; (ii) population: women aged 13–49 years, having menarche for at least a year; (iii) not post-menopausal women, pregnant women, women with genital pathologies, or women with serious pathologies (cancer); (iv) observational studies only.

2.4. Data Extraction and Data Synthesis

In the selected studies, certain data were extracted, in particular the objective and the type of study, the number and age of the participants and their specificity (sports or not) (Table 1). In addition, outcome measures such as ACL injury, laxity/stiffness of the knee and general joint laxity (GJL) were selected (Table 2).

Table 1. Studies included in this review.

Authors	Year	Objective	Type of Study	Participants	Age	Specificity	Study Quality
DeFroda et al. [25]	2019	To examine the effects of OC usage on ACL tear and subsequent reconstruction	Case-controls	82,874	15–49 years	Database	E
Gray et al. [26]	2016	To determine if women undergoing anterior cruciate ligament surgical reconstruction were less likely to use oral contraceptives than a matched noninjured population	Case-controls	12,819	15–39 years	Database	E
Herzog et al. [27]	2020	Quantifying the association between OC use and ACL injury	Cohort	2,992,084	13–45 years	Database	A
Khowailed et al. [28]	2015	Investigating the effects of 17 β -estradiol across phases of the menstrual cycle on neuromuscular control patterns of ACL laxity during running	transverse	12	25.6 $\pm$ 3.7 years	Runners	E
Lee et al. [29]	2015	To study the difference in ACL laxity after squat exercise in healthy women between OC users and non-OC users.	Cohort	40	25.2 $\pm$ 2.2 years	Low to moderate PA	E
Maruyama et al. [12]	2021	To determine the relationship between knee joint looseness, stiffness, and general joint looseness in relation to the menstrual cycle	transverse	15	21 $\pm$ 0.2 years	female students Low to moderate PA	E
Nose-Ogura et al. [30]	2017	To study the concentration of relaxin-2 during the menstrual cycle in athletes without and with OC.	transverse	106	22 $\pm$ 3 years	athletes	E
Shafiei et al. [9]	2016	Comparing knee laxity changes in the menstrual cycle in female athletes	transverse	40	25.5 $\pm$ 5.12 years	athletes	A
Shagawa et al. [31]	2021	To examine changes in AKL, stiffness, GR and GJL during the late follicular phase and ovulation	transverse	15	21 $\pm$ 0.3 years	E	E

Table 1. Cont.

Authors	Year	Objective	Type of Study	Participants	Age	Specificity	Study Quality
Stijak et al. [32]	2015	To determine the difference in testosterone, 17^{β} estradiol and progesterone concentrations between patients with and without ACL tear, and the possible effect of these hormones on generalized joint laxity	Case-controls	24	16–37 years	athletes	E

Abbreviations: OC, oral contraceptives; ACL, anterior cruciate ligament; AKL, anterior displacement of the tibia relative to the femur; GR, genu recurvatum; GJL, general joint laxity.

Table 2. Summary of included studies.

Authors	Variables Studied	Method of Measurement of Variables	ACL Tear	Contraceptive Method	Hormones Studied	Results
DeFroda et al. 2019 [25]	ACL injury	Follow-up over time	Case: surgical reconstruction of ACL with OC Controls: surgical reconstruction of ACL without OC	569 ACL reconstruction patients in the non-OC group, and 465 patients in the OC group.	/	OC users: 18% decrease in the risk of ACL tear requiring reconstruction OC users 15–19 age group: 63% reduction in tears
Gray et al. 2016 [26]	ACL injury	Follow-up over time	Case: surgical reconstruction of the ACL	12,819 OC	/	15–19 age group with ACL repair surgery: not use OC 1.22 times > controls (12 months prior to injury) ($p < 0.0001$) 25–39 age group: use OC 1.1 to 1.16 times > controls OC users: 18% fewer ACL injuries than non-users (15–19 age group)
Herzog et al. 2020 [27]	ACL injury	Follow-up over time	3571 at OC 1620 at IUD	OC (exposed) IUD (unexposed)	/	No difference in the risk of ACL injury in OCs and IUDs
Khowailed et al. 2015 [28]	Knee laxity [estradiol] Neuro-muscular control	KT-2000 Cobas e602 blood test (Roche/Hitachi) → EMG	No	No	Estradiol	↑ ATT: ovulation (5.75 ± 0.47) ($p < 0.01$) ↓ ATT: follicular (4.18 ± 0.27) ($p < 0.01$) [17^{β} estradiol] ↓ menstruation (34.14 ± 15.47 pg/mL) [17^{β} estradiol] ↑ ovulation (207.74 ± 53.42 pg/mL) [17^{β} estradiol] _{ovulation} > [17^{β} estradiol] _{follicular} ($p < 0.01$)
Lee et al. 2015 [29]	ACL laxity Pain	KT-2000 EVA	No	25 with normal cycle 15 with OC	/	Decreased ACL laxity (OC users) compared to non-OC users before and after strenuous exercise Pain after exercise (OC) > pain after exercise (non-OC)

Table 2. Cont.

Authors	Variables Studied	Method of Measurement of Variables	ACL Tear	Contraceptive Method	Hormones Studied	Results	
						GR	No GR
Maruyama et al. 2021 [12]	AKL Stiffness GJL GR	KS-measurement Δ force/ Δ displacement University of Tokyo joint laxity test Item 4 of the GJL test, goniometer	No	No	/	AKL (89N and 133N) Ovulatory phase > early follicular phase	No difference in AKL between phases
Nose-Ogura et al. 2017 [30]	[relaxin-2] [sex hormones]	Immunoassay (quantikin Human relaxin-2) CLIA kit	No	16 with OC 77 eumenorrhea 13 amenorrhea	relaxin-2 sex hormones	[relaxin-2] _{luteal} > [relaxin-2] _{follicular, ovulatory} in eumenorrhea [relaxin-2] at eumenorrhea > [relaxin-2] at OC luteal phase: [relaxin-2] > 6.0 pg/mL in 36.8% of FDR cases. ACL injury correlation between relaxin-2 and progesterone in CM phases except luteal phase	
Shafiei et al. 2016 [9]	Knee laxity (ACL) [sex hormones]	Lachman Front drawer ELISA and DEMEDITEC kit	No	No	[estrogen] [progesterone]	No difference for ACL laxity nor hormonal levels. No relationship between menstrual cycle phases and knee laxity	
Shagawa et al. 2021 [31]	AKL stiffness GJL GR [estradiol]	KS-measurement Δ force/ Δ displacement University of Tokyo joint laxity test Item 4 of the GJL test, goniometer Saliva sample Ovulation kit (+T° control: thermometer)	No	No	Estradiol	[oestradiol] _{ovulatory} > late follicular [oestradiol] ($p = 0.018$) No differences between AKL or rigidity of the follicular phase and the ovulatory phase GR and GJL $\uparrow$ during ovulatory phase > follicular phase Changes in [estradiol] during the cycle can affect changes in GR and GJL	
Stijak et al. 2015 [32]	GJL [sex hormones]	Laxity score (Beighton, Solomon, Soskolne) sample $\rightarrow$ enzyme immunoassay Salimetrics	Yes contactless (case) No (control)	No	[17 β estradiol] [progesterone] [testosterone]	Significant differences in [17 β estradiol], [progesterone], and [testosterone] between the two groups Lower [hormones] in women with ACL tears	

Abbreviations: OC, oral contraceptives; ACL, anterior cruciate ligament; IUD, intrauterine device; AKL, anterior displacement of the tibia relative to the femur; GR, genu recurvatum; GJL, general joint laxity; $\downarrow$ significant decrease; $\uparrow$ significant increase.

2.5. Risk of Bias Assessment

The assessment of article quality and risk of bias was performed using McMaster guidelines for Critical Review Form for Quantitative studies [33]. This guide is made up of 16 criteria: (1) objectives of the study clearly defined; (2) presentation of the relevant context; (3) design of the study appropriate; (4) sample described in detail; (5) sample size justified; (6) reliable measurement of variables; (7) valid measurement of variables; (8)

intervention described in detail; (9) contamination avoided; (10) co-intervention avoided; (11) intervention replicable; (12) results reported in terms of statistical significance; (13) methods analysis; (14) reported clinical importance; (15) loss and abandons reported; (16) appropriate conclusions regarding study methods and results. In this review, consisting exclusively of observational studies, criteria 9 and 10 (contaminations and co-interventions avoided) could not be evaluated. For each item, 1 point was given if it was completed and 0 when it was not answered. The quality score of each study was calculated on 14 criteria, 14 being the maximum score. Then, a classification according to the methodological quality was carried out in percentage form. When the total score was lower than 50% the quality was considered low, acceptable between 50% and 64%, high quality between 65% and 79%, and excellent when the result was above 80%.

3. Results

A total of ten articles was selected in this systematic review according to the inclusion and exclusion criteria (Tables 1 and 2). The steps in this data collection are represented in Figure 1. Among these ten studies, the sports levels of the women differed: four studies included athletes [9,28,30,32]; three others involved women doing low-to-moderate-intensity physical activity [12,29,31]; and the three remaining studies did not provide this information, as they were extracted from a database [25–27].

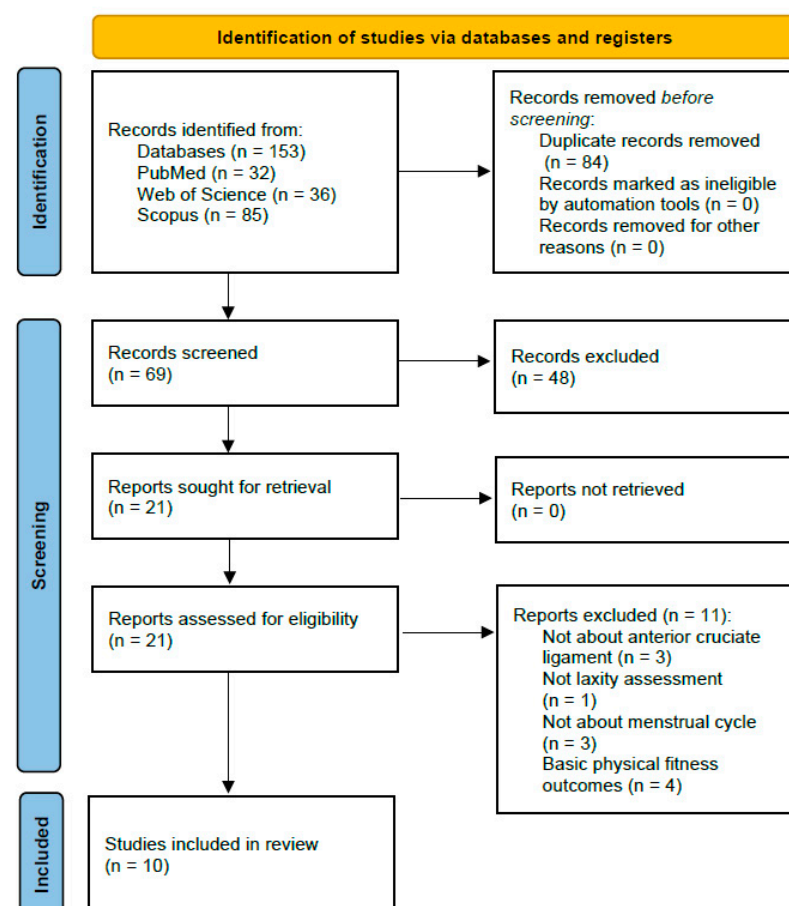


Figure 1. PRISMA Flow diagram.

The sample size ranged from 12 to 2,992,084 women aged 13–49 years old. The studies included in this review had scores based on the McMaster guidelines for Critical Review Form for Quantitative studies between 8/14 and 13/14. Three studies (30%) showed acceptable methodological quality, one (10%) high quality, and the other six (60%) were rated as excellent (Table 3).

Table 3. Quality Results methodology of the studies included in this review.

Article	Criteria															T	%	QM
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15			
Shagawa et al., (2021) [31]	1	1	1 (c)	1	0	1	1	1	N/A	1	1	1	1	1	1	13/14	93%	E
Maruyama et al., (2021) [12]	1	1	1 (c)	1	0	1	1	1	N/A	1	1	1	1	1	1	13/14	93%	E
Herzog et al., (2020) [27]	1	1	1 (a)	0	0	1	1	0	N/A	0	0	1	1	0	1	8/14	57%	A
DeFroda et al., (2019) [25]	1	1	1 (b)	0	0	1	1	0	N/A	0	1	1	1	0	1	9/14	64%	A
Nose-Ogura et al., (2017) [30]	1	1	1 (c)	1	0	1	1	1	N/A	1	1	1	1	1	1	13/14	93%	E
Gray et al., (2016) [26]	1	1	1 (b)	1	1	1	1	0	N/A	0	1	1	1	0	1	11/14	79%	H
Shafiei et al., (2016) [9]	1	1	1 (c)	1	0	1	1	0	N/A	0	1	1	0	0	0	8/14	57%	A
Lee et al., (2015) [29]	1	1	1 (a)	1	0	1	1	1	N/A	1	1	1	1	0	1	12/14	86%	E
Stijak et al., (2015) [32]	1	1	1 (b)	1	0	1	1	1	N/A	1	1	1	1	0	1	12/14	86%	E
Khowailed et al., (2015) [28]	1	1	1 (c)	1	1	1	1	1	N/A	1	1	1	1	0	1	13/14	93%	E
Total	8	8	8	7	1	8	8	6	/	6	7	8	7	3	7			

Abbreviations: 1: Objective of the study clearly defined; 2: Presentation of the relevant context; 3: Appropriate study design; 4: Sample described in detail; 5: Sample size justified; 6: Measurements of reliable variables; 7: Measurements of valid variables; 8: Intervention described in detail; 9: Contaminations and co-interventions avoided; 10: Replicable intervention; 11: Results reported in terms of statistical significance; 12: Appropriate analytical methods; 13: Reported clinical importance; 14: Reported Losses and Abandonments; 15: Appropriate conclusion regarding the methods and results of the study; T: total; %: Percentage of evaluation criteria completed; QM: Methodological quality; N/A: Not applied; E: Excellent; H: High quality; A: Acceptable; (a): cohort; (b): control cases; (c): transverse.

3.1. ACL Tears

Herzog et al., using a database, found no correlation between ACL injury risk and OC uses compared to an intrauterine device [27]. At the same time, the study conducted by Gray et al. demonstrated an 18% decrease in ACL reconstructions in OC users compared to non-users in the 15–19-year age group, with the mean age of cases being 24.11 years. In this group, women who had undergone ACL-repair surgery were 1.22 times more likely not to use OC than controls in the 12 months before the injury ($p < 0.001$) [26]. In this same guideline, De Froda et al. demonstrated a 63% reduction in ACL tear rate in OC users in the same age group (15–19-years) [25].

In the study carried out by Stijak et al., ACL tears were caused by an indirect mechanism (without contact) [34]. There were no significant differences in the joint laxity score between the participants with the ACL intact and the participants suffering an ACL tear [32].

3.2. Knee Laxity

Modulation of knee laxity during the menstrual cycle has been reported in five studies [9,12,28,29,31]. Laxity, illustrated as the anterior displacement of the tibia (AKL) relative to the femur, was assessed by different methods: an instrumental technique (KT2000, KS measurement), and orthopedics test (Lachman's test, and the University of Tokyo joint-laxity test). Khowailed et al. reported a statistically significant increase ($p < 0.01$) in tibial anterior translation (TAT) during the ovulatory phase compared to the follicular phase [28]. However, among non-genu-recurvatum patients (GR), no significant differences were observed between the phases of the menstrual cycle [12]. Similarly, Shagawa et al. revealed an increased generalized joint laxity (GJL) during the ovulatory phase compared to the follicular phase, but no differences were found between the two phases concerning stiffness or AKL [31]. Finally, Maruyama et al. did not observe significant differences in GJL between GR and non-GR [12]. Among users of OC, researchers noted a decreased ACL laxity [29].

3.3. Hormones

Hormonal fluctuations were measured in five articles using kit ovulatory and blood and saliva samples [9,28,30–32]. Two studies showed that the estradiol concentration during ovulation was significantly higher than during the follicular phase [28,31]. In addition, the concentrations of estradiol, progesterone and testosterone were significantly reduced in women with a torn ACL [32]. However, Shafei et al. did not observe significant differences between ACL laxity and hormonal levels [9]. Finally, during the luteal phase, the concentration of relaxin was greater than 6.0 pg/mL in 36.8% of cases, proving to be a risk factor for rupture of the ACL [30].

4. Discussion

This study provides novel research about the influence of the menstrual cycle and OC on knee laxity and ACL injuries. The menstrual cycle seems to influence knee laxity in women, the latter being higher during the ovulatory phase. However, current knowledge cannot yield conclusions about the influence of the menstrual cycle on the risk of ACL injury. OC may decrease the possibility of an ACL tear.

As demonstrated by Stijak et al., women with an ACL tear show a decrease in the concentration of testosterone, 17 β estradiol and progesterone. This hormonal drop could lead to ACL damage and could be considered a risk factor. This, therefore, raises questions about the protective action or lack thereof of hormones. Indeed, during the ovulatory phase, when estradiol concentration is maximal, joint stability would be negatively affected [35]. This estradiol peak during the ovulatory phase is confirmed in the study carried out by Khowailed et al. since the concentration of 17 β estradiol significantly increases during ovulation, compared to the follicular phase [28]. These findings are in accordance with the results of the study performed by Shagawa et al. [31].

Regarding knee laxity, an increase in TAT could be observed during the ovulatory phase compared to the follicular phase [28]. In this line, Shagawa et al. observed an increase in GJL during the menstrual cycle phase where estradiol is higher [31]. Therefore, it can be assumed that the increase in estrogen concentration would induce an increase in knee laxity characterized by TAT. In concordance, the review performed by Herzberg et al. in 2017 identified a higher ACL laxity during the ovulatory phase compared to the follicular phase [24].

The role of OC in regulating the menstrual cycle has been investigated in some studies [27,29,30]. Herzog et al. did not detect an increased risk of ACL injury in OC or intrauterine device (IUD) users, not allowing a protective effect to be established. Nevertheless, the control group (IUD) had exogenous hormones, so it would be interesting to study the difference with eumenorrheic women (women with a regular cycle and not taking OC). According to Nose Ogura et al. and Lee et al., OC users have decreased ACL laxity [29] due to a lower relaxin concentration [30], and therefore may have a lower risk of an ACL tear.

Consistent with these findings, the study carried out by Gray et al. suggests that the regulatory effects of OC on estrogen levels may reduce the overall risk of ACL injury in young women by reducing the risk factor for induced ACL laxity by estrogen [26]. Despite the limited clinical evidence on this protective aspect, De Froda et al. state that it would be advisable to consider the use of OC in elite high school and college-aged athletes, especially those who are at risk of ACL tear [25]. Future research is needed to confirm this protective association.

Some aspects should be considered when interpreting the results of this review. The age range of the participants is very wide, between 13 and 49 years old. In addition, the selected studies do not specify whether the participants had been pregnant before. During pregnancy, women suffer an important hormonal imbalance [36], so it would be wise to carry out studies on women who have never been pregnant to observe the true impact of a menstrual cycle without previous upheaval. It can be assumed that after pregnancy the hormonal levels are modified, in particular those of relaxin, so it would be interesting to observe whether there is an increased risk of ACL injury in postpartum women.

Another important aspect to consider is that the hormonal profile of each woman may differ during each cycle even in women with a regular menstrual cycle [37]. For this reason, measurement tools should be predefined identically in each study to avoid any bias in the evaluation of data, allowing researchers to perform a meta-analysis on this subject. The human body being very complex, it would be necessary to study the interaction of the various hormones and not their individual action. Stijak et al. have shown that a higher concentration of testosterone could act protectively for ACL injuries in women [32]. Interestingly, Lovering and Romani [10] demonstrated the presence of androgen receptors in the female ACL. In fact, testosterone, which plays a role in connective tissue remodeling, is influenced by the presence of other hormones. In fact, an increase in the sex-hormone-binding globulin (SHBG) levels is associated with decreased levels of testosterone. However, estrogen and testosterone have an antagonistic relationship. Higher rates of free testosterone have been correlated with an increase in ACL stiffness during the ovulatory phase [10]. Further research on this topic is needed.

Studies have observed changes in the menstrual cycle associated with physical activity levels [38]. Indeed, most women (>50%) practicing regular physical activity have menstrual dysfunction, characterized by an irregular menstrual cycle [36]. It would therefore be interesting to study the differences in knee laxity related to the menstrual cycle between physically active women and sedentary women.

Another factor that could exert a negative influence on the menstrual cycle is stress. Moreover, progesterone levels, which are higher during the luteal phase, may be associated with anxiety [39]. An increase in mental fatigue has also been observed during this phase [40], which could contribute to certain injuries, in particular the ACL, according to many studies [38].

The previous review published in 2015 by Somerson et al. revealed a greater anterior translation of the knee in the ovulatory and luteal phases of the menstrual cycle. In this current review, we find the same results, which seem consistent. However, no correlation was found between the risk of ACL rupture and periods of laxity.

Further studies are needed to observe the association between estrogen levels and knee joint laxity. Future research should be considered to observe the action of testosterone in women especially in sports. A better understanding of women's physiology is essential to injury prevention.

5. Conclusions

In conclusion, the menstrual cycle, due to hormonal fluctuation, seems to influence knee laxity in women. Female athletes have a higher risk of ACL rupture due to hormonal changes, especially relaxin. The increase in the latter was observed predominantly in the luteal phase parallel to estradiol during the ovulatory phase when the TAT was greater at the knee. On the other hand, OC decreased the laxity of the ACL, making the TAT weaker and decreasing the levels of relaxin, which appears to decrease the possibility of an ACL tear. However, based on the literature, we cannot conclude that there is a correlation between the menstrual cycle and the risk of ACL injury.

Author Contributions: J.M. and A.F., Conceptualization, data curation, formal analysis, writing—original draft; D.D.-B. and Á.G.-d.-I.-F., investigation, methodology, validation, writing—review & editing; J.S.-A., Conceptualization, methodology, supervision, validation; G.G.-P.-d.-S., methodology, supervision, validation, writing—review & editing. All authors have read and agreed to the published version of the manuscript.

Funding: The authors received no financial support for the research, authorship, and/or publication of this article.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Datson, N.; Drust, B.; Weston, M.; Jarman, I.H.; Lisboa, P.; Gregson, W. Match Physical Performance of Elite Female Soccer Players During International Competition. *J. Strength Cond. Res.* **2017**, *31*, 2379–2387. [\[CrossRef\]](#) [\[PubMed\]](#)
2. Datson, N.; Hulton, A.; Andersson, H.; Lewis, T.; Weston, M.; Drust, B.; Gregson, W. Applied physiology of female soccer: An update. *Sport. Med.* **2014**, *44*, 1225–1240. [\[CrossRef\]](#) [\[PubMed\]](#)
3. Gebert, A.; Gerber, M.; Pühse, U.; Gassmann, P.; Stamm, H.; Lamprecht, M. Costs resulting from nonprofessional soccer injuries in Switzerland: A detailed analysis. *J. Sport Health Sci.* **2020**, *9*, 240–247. [\[CrossRef\]](#)
4. Mufty, S.; Bollars, P.; Vanlommel, L.; Van Crombrugge, K.; Corten, K.; Bellemans, J. Injuries in male versus female soccer players: Epidemiology of a nationwide study. *Acta Orthop. Belg.* **2015**, *81*, 289–295. [\[PubMed\]](#)
5. Roos, K.G.; Wasserman, E.B.; Dalton, S.L.; Gray, A.; Djoko, A.; Dompier, T.P.; Kerr, Z.Y. Epidemiology of 3825 injuries sustained in six seasons of National Collegiate Athletic Association men's and women's soccer (2009/2010–2014/2015). *Br. J. Sports Med.* **2017**, *51*, 1029–1034. [\[CrossRef\]](#) [\[PubMed\]](#)
6. Somerson, J.S.; Isby, I.J.; Hagen, M.S.; Kweon, C.Y.; Gee, A.O. The Menstrual Cycle May Affect Anterior Knee Laxity and the Rate of Anterior Cruciate Ligament Rupture: A Systematic Review and Meta-Analysis. *JBJS Rev.* **2019**, *7*, e2. [\[CrossRef\]](#)
7. Larruskain, J.; Lekue, J.A.; Diaz, N.; Odriozola, A.; Gil, S.M. A comparison of injuries in elite male and female football players: A five-season prospective study. *Scand. J. Med. Sci. Sports* **2018**, *28*, 237–245. [\[CrossRef\]](#)
8. Lin, C.Y.; Casey, E.; Herman, D.C.; Katz, N.; Tenforde, A.S. Sex Differences in Common Sports Injuries. *PM&R* **2018**, *10*, 1073–1082.
9. Shafiei, S.E.; Peyvandi, S.; Kariminasab, M.H.; Azar, M.S.; Daneshpoor, S.M.M.; Khalilian, A.; Aghajantabar, Z. Knee Laxity Variations in the Menstrual Cycle in Female Athletes Referred to the Orthopedic Clinic. *Asian J. Sports Med.* **2016**, *7*, e30199. [\[CrossRef\]](#)
10. Lovering, R.M.; Romani, W.A. Effect of testosterone on the female anterior cruciate ligament. *Am. J. Physiol. Integr. Comp. Physiol.* **2005**, *289*, R15–R22. [\[CrossRef\]](#)
11. Gosselin, M. *Menstrual Cycle: Signs and Symptoms, Psychological/Behavioral Changes and Abnormalities: Signs and Symptoms, Psychological/Behavioral Changes and Abnormalities*; Nova Science Publishers Incorporated: Hauppauge, NY, USA, 2013.

12. Maruyama, S.; Yamazaki, T.; Sato, Y.; Suzuki, Y.; Shimizu, S.; Ikezu, M.; Kaneko, F.; Matsuzawa, K.; Hirabayashi, R.; Edama, M. Relationship Between Anterior Knee Laxity and General Joint Laxity During the Menstrual Cycle. *Orthop. J. Sports Med.* **2021**, *9*, 2325967121993045. [[CrossRef](#)] [[PubMed](#)]
13. Knudtson, J.; McLaughlin, J.E. *Endocrinologie de la Reproduction Féminine*; MSD Manuals: Rahway, NJ, USA, 2019.
14. Samuelson, K.; Balk, E.M.; Sevetson, E.L.; Fleming, B.C. Limited Evidence Suggests a Protective Association Between Oral Contraceptive Pill Use and Anterior Cruciate Ligament Injuries in Females: A Systematic Review. *Sports Health A Multidiscip. Approach* **2017**, *9*, 498–510. [[CrossRef](#)] [[PubMed](#)]
15. Nguyen, A.-D.; Shultz, S.J. Sex Differences in Clinical Measures of Lower Extremity Alignment. *J. Orthop. Sports Phys. Ther.* **2007**, *37*, 389–398. [[CrossRef](#)]
16. Shultz, S.J.; Sander, T.C.; Kirk, S.E.; Perrin, D.H. Sex differences in knee joint laxity change across the female menstrual cycle. *J. Sports Med. Phys. Fitness* **2005**, *45*, 594–603.
17. Beynon, B.D.; Bernstein, I.M.; Belisle, A.; Brattbakk, B.; Devanny, P.; Risinger, R.; Durant, D. The Effect of Estradiol and Progesterone on Knee and Ankle Joint Laxity. *Am. J. Sports Med.* **2005**, *33*, 1298–1304. [[CrossRef](#)] [[PubMed](#)]
18. Shultz, S.J.; Nguyen, A.-D.; Schutz, R.J. Differences in Lower Extremity Anatomical and Postural Characteristics in Males and Females Between Maturation Groups. *J. Orthop. Sports Phys. Ther.* **2008**, *38*, 137–149. [[CrossRef](#)] [[PubMed](#)]
19. Liu, S.H.; Al-Shaikh, R.; Panossian, V.; Yang, R.S.; Nelson, S.D.; Soleiman, N.; Finerman, G.A.M.; Lane, J.M. Primary immunolocalization of estrogen and progesterone target cells in the human anterior cruciate ligament. *J. Orthop. Res.* **1996**, *14*, 526–533. [[CrossRef](#)]
20. Yu, W.D.; Panossian, V.; Hatch, J.D.; Liu, S.H.; A Finerman, G. Combined Effects of Estrogen and Progesterone on the Anterior Cruciate Ligament. *Clin. Orthop. Relat. Res.* **2001**, *383*, 268–281. [[CrossRef](#)]
21. Karageanes, S.J.; Blackburn, K.; Vangelos, Z.A. The association of the menstrual cycle with the laxity of the anterior cruciate ligament in adolescent female athletes. *Clin. J. Sport Med.* **2000**, *10*, 162–168. [[CrossRef](#)]
22. Schmitz, R.J.; Shultz, S.J. Anterior knee stiffness changes in laxity “responders” versus “nonresponders” across the menstrual cycle. *J. Athl. Train.* **2013**, *48*, 39–46. [[CrossRef](#)]
23. Faryniarz, D.A.; Bhargava, M.; Lajam, C.; Attia, E.T.; Hannafin, J.A. Quantitation of estrogen receptors and relaxin binding in human anterior cruciate ligament fibroblasts. *Vitr. Cell. Dev. Biol. Anim.* **2006**, *42*, 176–181. [[CrossRef](#)] [[PubMed](#)]
24. Herzberg, S.D.; Motu’apuaka, M.L.; Lambert, W.; Fu, R.; Brady, J.; Guise, J.-M. The Effect of Menstrual Cycle and Contraceptives on ACL Injuries and Laxity: A Systematic Review and Meta-analysis. *Orthop. J. Sport. Med.* **2017**, *5*, 2325967117718781. [[CrossRef](#)] [[PubMed](#)]
25. DeFroda, S.F.; Bokshan, S.L.; Worobey, S.; Ready, L.; Daniels, A.H.; Owens, B.D. Oral contraceptives provide protection against anterior cruciate ligament tears: A national database study of 165,748 female patients. *Phys. Sportsmed.* **2019**, *47*, 416–420. [[CrossRef](#)] [[PubMed](#)]
26. Gray, A.M.; Gugala, Z.; Baillargeon, J.G. Effects of Oral Contraceptive Use on Anterior Cruciate Ligament Injury Epidemiology. *Med. Sci. Sports Exerc.* **2016**, *48*, 648–654. [[CrossRef](#)] [[PubMed](#)]
27. Herzog, M.M.; Young, J.C.; Lund, J.L.; Pate, V.; Mack, C.D.; Marshall, S.W. Oral contraceptive use and anterior cruciate ligament injury: Comparison of active comparator new user cohort and case-control study designs. *Inj. Epidemiol.* **2020**, *7*, 53. [[CrossRef](#)]
28. Khowailed, I.A.; Petrofsky, J.; Lohman, E.; Daher, N.; Mohamed, O. 17 β -Estradiol Induced Effects on Anterior Cruciate Ligament Laxness and Neuromuscular Activation Patterns in Female Runners. *J. Womens Health* **2015**, *24*, 670–680. [[CrossRef](#)]
29. Lee, H.; Petrofsky, J.S.; Yim, J. Do Oral Contraceptives Alter Knee Ligament Damage with Heavy Exercise? *Tohoku J. Exp. Med.* **2015**, *237*, 51–56. [[CrossRef](#)]
30. Nose-Ogura, S.; Yoshino, O.; Yamada-Nomoto, K.; Nakamura, M.; Harada, M.; Dohi, M.; Okuwaki, T.; Osuga, Y.; Kawahara, T.; Saito, S. Oral contraceptive therapy reduces serum relaxin-2 in elite female athletes. *J. Obstet. Gynaecol. Res.* **2017**, *43*, 530–535. [[CrossRef](#)]
31. Shagawa, M.; Maruyama, S.; Sekine, C.; Yokota, H.; Hirabayashi, R.; Hirata, A.; Yokoyama, M.; Edama, M. Comparison of anterior knee laxity, stiffness, genu recurvatum, and general joint laxity in the late follicular phase and the ovulatory phase of the menstrual cycle. *BMC Musculoskelet. Disord.* **2021**, *22*, 886. [[CrossRef](#)]
32. Stijak, L.; Kadija, M.; Djulejić, V.; Aksić, M.; Petronijević, N.; Marković, B.; Radonjić, V.; Bumbaširević, M.; Filipović, B. The influence of sex hormones on anterior cruciate ligament rupture: Female study. *Knee Surg. Sport. Traumatol. Arthrosc.* **2015**, *23*, 2742–2749. [[CrossRef](#)]
33. Law, M.; Stewart, D.; Pollock, N.; Letts, L.; Bosch, J.; Westmorland, M. *Guidelines for Critical Review Form—Quantitative Studies*; McMaster University Occupational Therapy Evidence-Based Practice Research Group: Hamilton, ON, Canada, 1998.
34. Bisciotti, G.N.; Chamari, K.; Cena, E.; Bisciotti, A.; Corsini, A.; Volpi, P. Anterior cruciate ligament injury risk factors in football. *J. Sports Med. Phys. Fitness* **2019**, *59*, 1724–1738. [[CrossRef](#)] [[PubMed](#)]
35. Sung, E.-S.; Kim, J.-H. The influence of ovulation on postural stability (Biodex Balance System) in young female. *J. Exerc. Rehabil.* **2018**, *14*, 638–642. [[CrossRef](#)] [[PubMed](#)]
36. Noyola-Martínez, N.; Halhali, A.; Barrera, D. Steroid hormones and pregnancy. *Gynecol. Endocrinol.* **2019**, *35*, 376–384. [[CrossRef](#)] [[PubMed](#)]
37. Hackney, A. *Sex Hormones, Exercise and Women*, 1st ed.; Springer: Cham, Switzerland, 2017; pp. 113–138.

38. Orio, F.; Muscogiuri, G.; Ascione, A.; Marciano, F.; Volpe, A.; La Sala, G.; Savastano, S.; Colao, A.; Palomba, S. Effects of physical exercise on the female reproductive system. *Minerva Endocrinol.* **2013**, *38*, 305–319.
39. Reynolds, T.A.; Makhanova, A.; Marcinkowska, U.M.; Jasienska, G.; McNulty, J.K.; Eckel, L.A.; Nikonova, L.; Maner, J.K. Progesterone and women's anxiety across the menstrual cycle. *Horm. Behav.* **2018**, *102*, 34–40. [[CrossRef](#)]
40. Nillni, Y.I.; Toufexis, D.J.; Rohan, K.J. Anxiety sensitivity, the menstrual cycle, and panic disorder: A putative neuroendocrine and psychological interaction. *Clin. Psychol. Rev.* **2011**, *31*, 1183–1191. [[CrossRef](#)]