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# Effect of Menstrual Cycle Phase on Exercise-Induced Muscle Damage

Bachelor's project in Movement science Supervisor: Dionne Noordhof May 2021

NTNU Norwegian University of Science and Technology Faculty of Medicine and Health Sciences Department of Neuromedicine and Movement Science

**Bachelor's project** 



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#### Abstract

**Purpose:** Exercise can result in muscle damage, known as exercise-induced muscle damage (EIMD). It is currently unclear if sex hormone fluctuations during the menstrual cycle (MC) affect EIMD. The purpose of this literature review was therefore to investigate the effect of MC phase on EIMD. **Methods:** A literature search was conducted in the databases PubMed and SPORTDiscus using the search terms "Menstrual Cycle", "Menses", "luteal", "follicular", "Muscle Damage", "EIMD", "muscle soreness", and "DOMS". Studies had to investigate EIMD in healthy, trained females during at least two different MC phases using a within-subject study design to be included in the analysis. **Results:** A total of eight studies were included. Five studies found no significant effect of MC phase on EIMD. Two studies found significantly greater EIMD during the mid-follicular phase (MFP) compared to the mid-luteal phase (MLP) of the MC, and one during premenstrual phase compared to late-follicular phase and MLP. **Conclusions:** Due to inconsistent findings between the studies, no clear conclusion can be drawn regarding the effect of MC phase on EIMD. There is a need for more research with a standardized methodological approach to answer the research question.

**Bakgrunn:** Trening kan resultere i muskelskade, kjent som exercise-induced muscle damage (EIMD). Det er foreløpig uklart om kjønnshormonsvingninger i løpet av menstruasjonssyklusen (MC) påvirker EIMD. Formålet med denne litteraturstudien var derfor å undersøke effekten av MC-fase på EIMD. **Metode:** Et litteratursøk ble utført i databasene PubMed og Sportdiscus ved å bruke søkeordene «Menstrual Cycle», «Menses», «luteal», «follicular», «Muscle Damage», «EIMD», «muscle soreness», og «DOMS». Studier måtte undersøke EIMD hos friske, trente kvinner i minst to forskjellige MC-faser med et innen-gruppe studiedesign for å bli inkludert i analysen. **Resultat:** Åtte studier ble inkludert. Fem studier fant ingen signifikant effekt av MC-fase på EIMD. To studier fant signifikant mer EIMD i midtfollikulærfase (MFP) sammenlignet med midt-luteal fase (MLP) i MC, og en i premenstruell fase sammenlignet med senfollikulær fase og MLP. **Konklusjoner:** På grunn av inkonsekvente funn mellom studiene, kan ingen klar konklusjon trekkes angående effekten av MC-fase på EIMD. Det er behov for mer forskning med en standardisert metodisk tilnærming for å svare på forskningsspørsmålet.

**Keywords:** • delayed-onset muscle soreness • muscle damage • recovery • hormonal fluctuations • follicular phase • luteal phase

## 1. Introduction

Although the gap between sexes in participation in exercise science research is decreasing, women are still underrepresented (1). As a result, less is known about female physiology and its effect on aspects of exercise. The complexity of the menstrual cycle (MC) may be a reason for the underrepresentation in studies. The MC is often controlled for in exercise studies that include women, frequently by testing females when their sex hormone levels are at the lowest, usually during the early follicular phase (EFP) of the MC. Controlling for the MC in this way does not add to the body of knowledge about how the MC potentially affects aspects of exercise training in women, such as exercise performance, adaptation and recovery.

The median MC length is 28 days with most cycles lasting 25-30 days in eumenorrheic women and is broken down into two 14-day phases (2). Day 1-14 is called the follicular phase (FP), and day 15-28 is the luteal phase (LP). Ovulation marks the end of the FP and the start of the LP. Estradiol (E2) and progesterone (P4) are important sex hormones which fluctuate across the MC. Both hormones are at their lowest level during the early follicular phase (EFP), followed by a peak in E2 in the late follicular phase (LFP) before E2 levels off while P4 reaches its peak in the mid luteal phase (MLP) (see figure 1) (3). A new cycle begins with menstruation, marking the end of the LP and beginning of the FP.

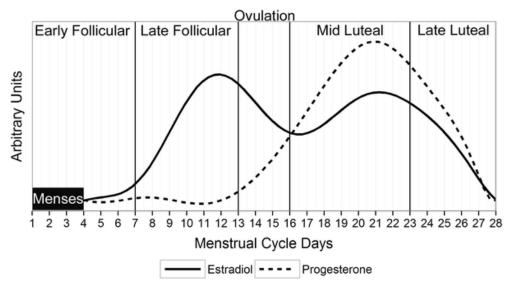


Figure 1: Estradiol and progesterone fluctuations across the menstrual cycle. Menstrual cycle phases with ovulation in the middle that divides the follicular and luteal phase. Reprinted from Tenan, M.S., Hackney, A.C. & Griffin, L. Maximal force and tremor changes across the menstrual cycle. Eur J Appl Physiol **116**, 153–160 (2016). <u>https://doi.org/10.1007/s00421-015-3258-x</u>. Copyright © 2015, Springer-Verlag Berlin Heidelberg (outside the USA)

Conflicting results are often reported in studies researching the effect of the MC on aspects of training and performance (4). This may partly be due to methodological issues and differences in how the phases of the MC are identified (5). One of the difficulties around identifying MC could be that many physically active females suffer from anovulation and luteal phase deficiency (LPD). As many as 30% of the physically active females can suffer from these conditions and the number can rise to 50% depending on the amount of exercise (>450 minutes per week) (5). Women with these conditions have reduced E2 and P4 production (5).

In recent years, the effect of the MC on exercise has received more attention in exercise science. Training performance in different phases of the MC is one of the topics which has received the most attention. A recent systematic review and meta-analysis by McNulty et al. (4) on the effect of MC phase on training performance included 78 studies. Of the included studies, 24% were allocated a quality rating of moderate, and only 8% were allocated a high rating, with respects to their methodological approach to identifying and verifying MC phase. The authors reported that training performance may be trivially reduced during the EFP. However, they also noted that due to the quality of the included studies, large between-study variation and low effect size, the results should be taken with caution.

Exercise can result in exercise-induced muscle damage (EIMD), which requires recovery. The extent of the damage can range from a few macromolecules to large tears in the sarcolemma, basal lamina, and supportive connective tissue, and to damage in the contractile and cytoskeletal proteins of the muscle fiber (6). This damage leads to regenerative events which are required for recovery and can last up to as much as 14 days, depending mainly on training status, exercise modality, duration and intensity (7). EIMD can become apparent to the athlete as reduced athletic performance and/or delayed onset muscle soreness (DOMS), which is usually felt as pain and stiffness after exercise which peaks within 24-72 hours (8). DOMS can be used as a subjective, indirect marker of EIMD and is usually rated on a scale, such as the visual analog scale (9).

Creatine kinase (CK) and myoglobin are commonly used as indirect markers of EIMD (10). In addition, interleukin-6 (IL-6) is an inflammatory cytokine involved in increased protein degradation and satellite cell proliferation which may aid muscle regeneration after exercise (11).

The female sex hormone oestrogen is of interest, as there is evidence to suggest it may play a role in reducing EIMD and potentially in muscle repair (12, 13). Progesterone is another sex

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hormone and may act antagonistically to oestrogen in some respects. For example, oestrogen suppresses protein catabolism while progesterone promotes it (14).

Although there is considerably less research regarding MC phase and recovery from exercise, some has been conducted. Hackney et al. (15) found greater CK activity in the MFP compared to MLP at 24- and 72-hours after exercise. A study by Markofski et al. (16) found greater CK activity 96-hours after exercise in the LP group compared with the FP group. This study compared groups, which is a limitation as large inter-individual variability in CK response to exercise is common (17). In contrast, Romero-Parra et al. (18) found no significant difference in any marker of EIMD between MC phases.

As outlined above, there is a theoretical basis to hypothesize that EIMD could differ in both magnitude and time required to recover depending on MC phase. Studies on the topic, however, report conflicting results. Therefore, the goal of this review paper is to investigate the effect of MC phase on EIMD.

### 2. Method

A literature search of relevant studies was conducted using the databases PubMed and SPORTDiscus. The keywords used in this literature search were "Menstrual Cycle", "Menses", "luteal", "follicular", "Muscle Damage", "EIMD", "muscle soreness" and "DOMS". The Boolean operators "OR" and "AND" were used in both search engines. The synonyms were combined in the search with "OR", and then the MC words were combined with the muscle damage words with "AND". In PubMed the search was done using the field option, selecting "Title/Abstract". Figure 2 outlines the literature search process.

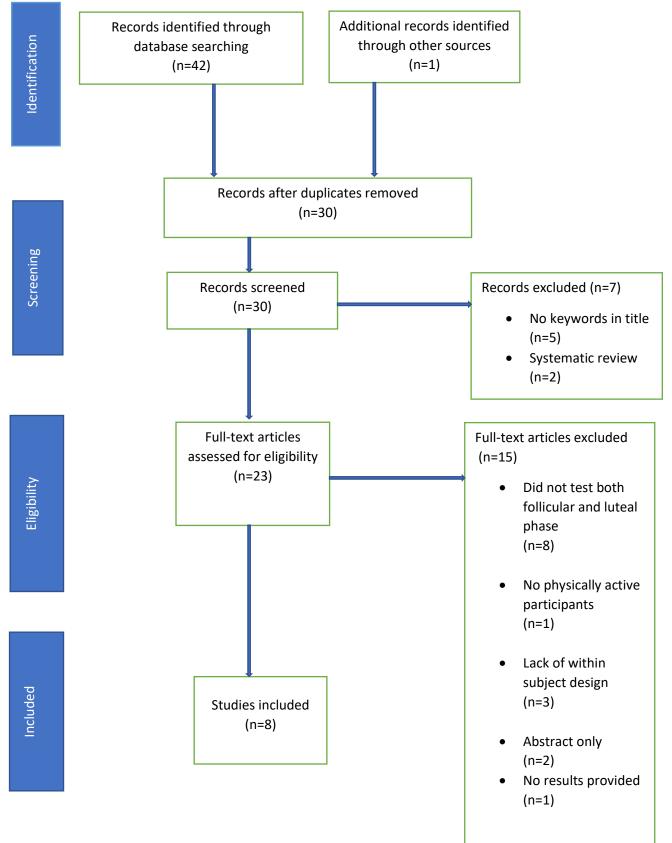


Figure 2: literature search process of included/excluded studies

## 3. Results

Eight studies (15, 18-24) were included with a total of 104 physically active subjects with an average age of 25 years. Characteristics of the studies are represented in table 1. The biomarkers that were included to investigate EIMD in different MC phases were CK, myoglobin, DOMS and IL-6. One of the studies used both strength training and cycling to induce muscle damage, three used running, one used cycling, and the remaining three performed strength training. All the included studies analyzed serum blood samples to verify MC phase.

Author s	n	Subjects (age (years), training status)	Exercise modality	Exercise intensity	Exercise volume	Time between exercise sessions	MC determination and verification	Exercise day after onset of menses	Estrogen (pg/ ml)	Progesterone(ng/m l)
Chaffin et al. (2013)	9	$26.8 \pm 4$ , runners	Flat running	50-110% VO <sub>2peak</sub>	75 min	-	Calendar-based BBT Blood samples of E2 + progesterone	EFP: 1-3 MLP: 20-22	EFP: 68.44 ± 28.73 MLP: 85.78 ± 14.75	EFP: 8.70 ± 3.42 MLP: 13.73 ± 2.54
Graja et al. (2020)	10	22.5 ± 1, handball players	Leg extension Cycling	MVC Max effort	20 x 5s, pause: 25s	8-15 days	Calendar-based Ovulation test tape Blood samples of E2 + progesterone	LFP: 11-13 MLP: 21-23 PMP: 28-29	LFP: $386.91 \pm 31.88$ MLP: $194 \pm 6.02$ PMP: $77.48 \pm 6.49$	LFP: $0.54 \pm 0.18$ MLP: $14.61 \pm 1.68$ PMP: $1.77 \pm 0.62$
Hackne y et al. (2019)	8	25 ± 4, trained female runners	Running	70% of VO <sub>2max</sub>	90 min	-	Calendar-based Blood samples of E2 + progesterone	MFP: 8 ± 2 MLP: 23 ± 3	MFP: 23.8 ± 6.6 MLP: 134.3 ± 38.8	MFP: 1.1 ± 0.4 MLP: 6.7 ± 3.9
Kłapciń ska et al. (2002)	7	21 ± 1.1, healthy physical activity students	Cycling	VO <sub>2max</sub>	Starting at 30W 3 min>increases progressively 30W every 3 min till exhausted	About 1 month apart (length of 1 MC)	BBT Blood samples of E2 + progesterone	MFP: 6-8 MLP: 4-6 days after ovulation	MFP: 50.83 ± 13.97 MLP: 105.88 ± 11.82	MFP: 2.03 ± 0.16 MLP: 37.17 ± 2.51

Table 1: Characteristics of the included studies.

McKinl ey- Barnard et al. (2018)	22	20.9 ± 1.4, physically active	Unilateral, iso- kinetic, eccentric knee extensions	30% of predetermin ed maximal voluntary initiation of contraction	10x10	-	Calendar-based Blood samples of E2	MFP: 6 MLP: 21	MFP: 15.36 ± 9.58 MLP: 18.43 ± 13.81	-
Romero -Parra, Alfaro- Magalla nes, et al (2020)	19	28.6 ± 5.9, well- trained	Squats	60% of 1RM	10x10	Minimu m of 1 week: two menstru al cycles to finish the 3 exercise sessions	Calendar-based Gynecologist determined the subject's cycle phases and average phase length Urine test to detect luteinizing hormone, in the 3-5 days before the expected ovulation date Blood samples of E2 + progesterone	EFP: - LFP: - MLP: -	EFP: 38.2 ± 32.1 LFP: 185.1 ± 173.9 MLP: 156.1 ± 91.5	EFP: 0.3 ± 0.1 LFP: 0.4 ± 0.7 MLP: 10.1 ± 3.9
Romero -Parra, Barba- Moreno, et al. (2020)	19	28.6 ± 5,9, well- trained	Squats	60% of 1RM	10x10	Minimu m of 1 week: two menstru al cycles to finish the 3 exercise sessions	Calendar-based Gynecologist determined the subject's cycle phases and average phase length Urine test to detect luteinizing hormone, in the 3-5 days before the expected ovulation date Blood samples of E2 + progesterone	EFP: - LFP: - MLP: -	EFP: 38.2 ± 32.1 LFP: 185.1 ± 173.9 MLP: 156.1 ± 91.5	EFP: $0.3 \pm 0.1$ LFP: $0.4 \pm 0.7$ MLP: $10.1 \pm 3.9$
William s et al. (2015)	10	$21 \pm 1$ , highly trained	Running	VO <sub>2peak</sub>	Ranged between 12:35 to 16:10 min:s	-	Calendar-based Blood samples of E2	MFP: 7 ± 2 MLP: 23 ± 3	MFP: 39.8 ± 18.3 MLP: 148.1 ± 35.2	-

BBT= body basal temperature, EFP= early follicular phase, MLP= mid-luteal phase, MVC= maximum voluntary contraction, PMP= pre-menstrual phase (defined as late luteal phase, day ~23-28), W= watt, E2= estradiol, -= missing data, 1 RM= 1 repetition maximum

Authors	CK (U/L)		DOMS (1-10)	Myoglobin (µg·L)	IL-6 (pg/mL)		
Chaffin et al. (2013)	-		Combined mean (SD) of 24 hand 48 h after exerciseEFPMLP $4.67 \pm 2.14$ $3.67 \pm 1.64$	-	<b>EFP</b> Pre: ~0.7 ± 0.9 IP: ~4.2 ± 5.3	MLP ~0.7 ± 1.3 ~6.1 ± 6.0	
			No significant difference between phases at 24h or 48h				
Graja et al. (2020)	LFP	MLP	-	-	-		
(2020)	Rest: 99.75± 10.12	98.77±8.79					
	3 min: 113.59±12.38	119.12±7.75					
	РМР						
	Rest: 99.45±9.15						
	3 min: 127.2±11.54*						
Hackney et	MFP	MLP	-	-	MFP	MLP	
al. (2019)	Rest: 89.7 ± 16.7 IP: 109.7 ± 10.7 24h: 510.8* ± 344.9 72h: 425.7* ± 249.7	$92.6 \pm 9.6$ 112.7 ±16.8 275.1±55.1 211.2±23.4			Rest: $1.4 \pm 1.9$ IP: $24.9^* \pm 13.2$ $24h$ : $10.3^* \pm 7.1$ $72h$ : $4.3^* \pm 3.1$	$\begin{array}{c} 1.2 \pm 0.5 \\ 13.5 \pm 6.2 \\ 5.0 \pm 3.0 \\ 0.9 \pm 0.3 \end{array}$	
Kłapcińska et al. (2002)	MFP Rest: 73.8 ± 4.8 3 min: 76.2 ± 5.0 1h: 79.1 ± 5.1	MLP 70.6 ± 4.2 76.3 ± 4.1 79.9 ± 7.0	-	-	-		
	24h: $78.5 \pm 4.1$	$74.4\pm5.5$					

McKinley- Barnard et al. (2018)	-		No information ab measurements were		No information a measurements we		-	
al. (2018)			MFP	MLP	MFP	MLP		
			$\sim 2.5 \pm 2.4$	~2.4 ± 2.3	~36 ± 47	~18±4		
Romero- Parra, Alfaro- Magallanes, et al (2020)	-		<b>EFP</b> Rest: $\sim 0.4 \pm 0.7$ 24 h: $\sim 2.5 \pm 1.5$ 48 h: $\sim 1.8 \pm 1.1$ <b>MLP</b> Rest: $\sim 0.2 \pm 0.8$	LFP ~0.1 ± 0.3 ~3 ± 1.2 ~2.9 ± 1.6	-		-	
			Rest: $\sim 0.2 \pm 0.8$ 24 h: $\sim 3.1 \pm 1.3$ 48 h: $\sim 2.2 \pm 1.6$					
Romero-	MLP	LFP	-		MLP	LFP	MLP	LFP
Parra, Barba-	Rest: 100.7 ± 29.9	105.7 ± 33.1			Rest: 60.1 ± 10.6	$60.4 \pm 7.2$	Rest: 1.6 ± 0.3	$1.7\pm0.5$
Moreno, et al. (2020)	2 h: 150.6 ± 43.8	$155.1\pm44.9$			2 h: 107.9 ± 41.2	$129.1 \pm 56.3$	2 h: 2 ± 1.3	$1.7\pm0.6$
ui. (2020)	24 h: 172.1 ± 85.8	$195.5\pm95.3$			24 h: 66.1 ± 10.7	$64.9 \pm 7.9$	24 h: 1.5 ± 0	$1.7\pm0.7$
	48 h: 128.8 ± 49.5	$130.6\pm47.7$			48 h: 62.2 $\pm$ 8.1	$63.8 \pm 9$	48 h: 1.5 ± 0.1	$1.9\pm0.7$
	EFP				EFP		EFP	
	Rest: 108.6 ± 48				Rest: 62.8 ± 8.2		Rest: 1.7 ±0.7	
	2 h: 151.6 ± 70				2 h: 105.5 ± 43.9		2 h: $1.8 \pm 0.7$	
	24 h: 154.1 ± 69.3				24 h: 64.5 ± 9.6		24 h: 1.6 ± 0.2	
	48 h: 117.3 ± 40.1				48 h: 59.8 ± 7.4		48 h: 1.6 ± 0.5	
Williams et al. (2015)	MFP Rest: 106.8 ± 34.5 IP: 129.9± 38.0 30 min:161.2±60.9 24h: 378.7±176.5*	118.6±18.7 153.4±28.9	-		-		-	

CK= creatine kinase, DOMS= delayed onset muscle soreness, IL-6= Interleukin-6, -= not measured, EFP= early follicular phase, MLP= mid-luteal phase, Pre= before test, IP= immediately post exercise, PMP= pre-menstrual phase, MFP= mid-follicular phase, \*= significantly higher than other menstrual cycle phases at same measurement time (P <0.05)

Five of the included studies found no significant difference between MC phases for any of the relevant markers (CK, IL-6, DOMS, myoglobin) of EIMD, regardless of measurement time (18, 19, 21-23).

Three of the eight studies found significant differences in the amount of muscle damage between MC phases at some point in time after exercise (15, 20, 24). Williams et al. (24) and Hackney et al. (15) found significantly greater CK levels 24 h after exercise during MFP compared to MLP. Hackney et al. (15) also found significantly greater IL-6 levels at 24 h and CK and IL-6 levels at 72 h after exercise during MFP compared to MLP. Neither study found significant differences at other time points. Graja et al. (20) found CK to be significantly higher during pre-menstrual phase (PMP) which was defined as day ~23-28 of the MC compared to LFP and MLP 3 min after exercise.

### 4. Discussion

The purpose of this literature review was to investigate the effect of the different MC phases on EIMD after exercise. Eight studies met our criteria and were included (15, 18-24). Five studies found no significant effect of MC phase on EIMD and IL-6 (18, 19, 21-23). Two of the studies found significantly higher levels of muscle damage during the MFP compared to the MLP (15, 24), while one study found greater levels of CK after exercise during PMP compared to LFP and MLP, but no significant difference between LFP and MLP (20).

The MFP of the MC is characterized by low concentrations of both estrogen and progesterone, which contrasts with the MLP in which estrogen and progesterone levels are high. The two studies which found significantly greater CK in the MFP compared to MLP supports the hypothesis that higher sex hormone levels may reduce EIMD. Interestingly, none of the studies which included the LFP and MLP found any difference between these two MC phases. The LFP is characterized by peak estrogen- and low progesterone levels. The lack of difference between those MC phases may indicate that if estrogen levels are high, progesterone levels do not impact EIMD to a meaningful extent.

A recent meta-analysis published in February of 2021 investigated the effect of the MC phases (EFP, LFP and MLP) on EIMD (25). They found no significant difference in the CK response after exercise between MC phases. However, they concluded DOMS to be more severe 24-72 h after exercise during the EFP than MLP and LFP. This contrasts with the results of the studies included in this literature review, which found no significant difference in DOMS at any point in time between MC phases. A reason for this may be that they performed a meta-analysis which increases statistical power.

#### 4.1 Study Design and Sample Size

All the studies included in this review use a within-subject design, which has greater statistical power than between-subject design. None of the included studies tested subjects more than once in the same MC phase. The sample size in the included studies was mostly low. Five of the eight studies had a sample size of 10 participants or less (15, 19-21, 24). Chaffin et al. (19) found a trend for greater DOMS in the EFP than MLP, but it did not reach statistical significance. They hypothesized that a reason for this may be due to their small sample size which could result in the study being underpowered to detect a statistically significant difference. Interestingly, the three studies that found a significant difference at some point in time had a sample size of 10 or less, contrary to the three studies with the largest sample sizes which found no significant difference at any point in time.

#### 4.2 Exercise Modality

Kłapcińska et al. (21) used cycling as their sole exercise modality. Cycling involves primarily concentric muscle actions, which causes less muscle damage than eccentric work (26). The subjects in their study had notably lower CK levels 24 h after exercise than subjects in any of the other studies which measured CK at the same point in time after exercise. The CK levels in this study barely increased after exercise, with a mean increase from rest to 24 h after exercise in the MFP of the MC of ~6.3%, compared to a ~569% increase in the study by Hackney et al. (15). As such, their exercise protocol may not have been appropriate for the goal of inducing the amount of muscle damage required to detect a difference between MC phases. The two studies which

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found a significant difference between phases in CK after exercise also had the largest CK increase, as can be seen in table 2. This may indicate that the exercise protocol in the other studies which found no significant difference in EIMD between MC phases was unable to induce adequate muscle damage for a statistically significant difference to be detected. It could also be hypothesized that a difference in muscle damage between phases only occurs when the amount of muscle damage is high. Further research may be warranted to answer this question.

#### 4.3 Repeated Bout Effect

Performing an exercise session reduces muscle damage of a subsequent exercise session, which is known as the repeated-bout effect (RBE). This effect may last up to at least nine weeks (27). While the RBE may be lower in a trained population as they are already adapted, the RBE may still occur after unaccustomed exercise (28). Of the studies that specified the time between sessions, the lowest was one week and the longest was approximately one month. The other studies probably completed their sessions within one to two menstrual cycles depending on which phase the first session was performed in. This may affect the results as the first session is likely to have induced the most muscle damage. This was somewhat controlled for since all the studies randomized which MC phase each individual performed the first exercise session in. However, an RBE effect would increase intra-individual variability, which would reduce the probability of detecting a difference between MC phases due to a larger spread in the data. One of the studies accounted for this by performing unilateral strength exercise, training one leg the first session and the contralateral the next session. However, a contralateral RBE may exist, but the effect seems lower than after bilateral exercise (29). Studies with low statistical power may therefore benefit from performing unilateral exercise and have extended time between sessions to increase the likelihood of detecting a difference if there is one.

#### 4.4 Menstrual Cycle Phase Verification and Identification

All the studies in this review took blood samples to verify the correct MC phase. However, McKinley et al. (22) and Williams et al. (24) did not measure progesterone levels, only estrogen. As mentioned in the introduction, up to 30% of women can suffer from LPD and anovulation. Therefore, not measuring progesterone may have resulted in a failure to exclude women with LPD from these two studies. Additionally, Janse De Jonge et al. (5) recommends excluding data of participants with progesterone levels above 5 ng/mL (16 nmol/L) during LFP and below 5 ng/mL during MLP to ensure all participants have regular ovulatory MC phases. To the best of our knowledge, only two of the included studies reported excluding data from subjects not meeting this criterion (18, 23). Chaffin et al. (19) reported an average progesterone level of 8.70  $\pm$  3.42 ng/mL during the EFP, and Hackney et al. reported an average progesterone level of 6.7  $\pm$  3.9 during the MLP. Firstly, an average progesterone level above 5 ng/mL during the EFP is problematic, as progesterone is expected to be lower during EFP than LFP (5). Secondly, an average progesterone level of 6.7  $\pm$  3.9 during the MLP suggests that some subjects had a progesterone level of 5 ng/mL. This indicates that some subjects were likely either tested in the wrong MC phase or had an irregular MC in both studies. This could reduce the validity of the four studies mentioned in this paragraph regarding the effect of MC phase on EIMD (5).

#### 4.5 Measurement time

Timing and number of measurements differed between the studies. Graja et al. (20) performed their last measurement 3 min after exercise, while Hackney et al. (15) took their last measurement 72 h after exercise. This is of importance as markers of EIMD such as CK may reach peak level up to hours to days after an exercise session. A study on resistance trained men performing eccentric exercise found a peak in CK 24 h after exercise (8). Measuring not more than three min after exercise may therefore not be representative of the amount of EIMD, as it does not show the CK response in its entirety. Compared to Kłapcińska et al. (21), the CK response three min after exercise in Graja et al. (20) was larger. It is therefore possibly that their exercise protocol was sufficient to elicit high amounts of muscle damage, which could have shown a difference between MC phases similar to the other studies with the highest CK response, if more measurements were taken at a later point in time.

#### 4.6 DOMS

Three of the included studies used DOMS as an indirect marker of muscle damage. The study by Romero-Parra et al. (23) used it as their sole marker of muscle damage. This is problematic as DOMS is often not representative of the magnitude of EIMD, and changes in direct markers of muscle damage may occur without DOMS (30).

#### 4.7 Suggestions for future research

Due to the inconsistent findings, future research is warranted to answer the research question. The methodological approach in future studies should be standardized to increase the likelihood of answering the question while also allowing for better comparison between studies. For identifying and verifying MC phases, the recent recommendations of Janse de Jonge et al. (5) and Elliott-Sale et al. (31) should be followed. If statistical power is low, strength exercise may be preferable as it easily allows for unilateral training, which reduces the RPE. Additionally, the exercise protocol should be severe enough to induce sufficient muscle damage. This is especially important when researching a trained population, as they are more resistant to muscle damage. It is also important to include enough measurement times after exercise. A minimum of 24 h is advised in a trained population to reach peak levels of CK and other muscle damage markers, but longer time would be required to investigate whether there is a difference in time to recover to baseline values. CK may be a preferable marker compared to for example DOMS, as it is both objective and widely used.

#### 4.8 Practical Applications

Due to the inconsistent results between the studies, one should apply caution when attempting to extrapolate the results into practical application. Two studies found greater EIMD during the MFP than MLP, and one during the PMP compared to LFP and MLP. Female athletes are therefore advised to pay extra attention to the recovery phase during the MFP and/or PMP, as recovery seems inhibited. This may necessitate a reduction in training volume during these phases to accommodate the greater EIMD. Since the results of the included studies were mixed, this should be done on an individual basis as it is also plausible that MC phase has no effect on EIMD.

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## 5. Conclusions

It is difficult to arrive at clear conclusions regarding the effect of MC phase on EIMD after exercise. The results of the included studies in this literature review are inconsistent, which may be due to methodological differences, such as using different exercise protocols, measurement times and markers of EIMD. A more standardized methodological approach would be necessary in future research to answer the research question.

## 6. Reference List

1. Bruinvels G, Burden RJ, McGregor AJ, Ackerman KE, Dooley M, Richards T, et al. Sport, exercise and the menstrual cycle: where is the research? British Journal of Sports Medicine. 2017;51(6):487-8.

2. Reed BG, Carr BR. The Normal Menstrual Cycle and the Control of Ovulation: MDText.com, Inc., South Dartmouth (MA); 2000 2000.

3. Tenan MS, Hackney AC, Griffin L. Maximal force and tremor changes across the menstrual cycle. European Journal of Applied Physiology. 2016;116(1):153-60.

4. McNulty KL, Elliott-Sale KJ, Dolan E, Swinton PA, Ansdell P, Goodall S, et al. The Effects of Menstrual Cycle Phase on Exercise Performance in Eumenorrheic Women: A Systematic Review and Meta-Analysis. Sports Med. 2020;50(10):1813-27.

5. Janse DEJX, Thompson B, Han A. Methodological Recommendations for Menstrual Cycle Research in Sports and Exercise. Med Sci Sports Exerc. 2019;51(12):2610-7.

6. Schoenfeld BJ. The mechanisms of muscle hypertrophy and their application to resistance training. J Strength Cond Res. 2010;24(10):2857-72.

7. Owens DJ, Twist C, Cobley JN, Howatson G, Close GL. Exercise-induced muscle damage: What is it, what causes it and what are the nutritional solutions? European Journal of Sport Science. 2019;19(1):71-85.

8. Hackney KJ, Engels H-J, Gretebeck RJ. Resting Energy Expenditure and Delayed-Onset Muscle Soreness After Full-Body Resistance Training With an Eccentric Concentration. The Journal of Strength & Conditioning Research. 2008;22(5).

9. Cleather DJ, Guthrie SR. Quantifying delayed-onset muscle soreness: a comparison of unidimensional and multidimensional instrumentation. J Sports Sci. 2007;25(8):845-50.

10. Brancaccio P, Lippi G, Maffulli N. Biochemical markers of muscular damage. Clin Chem Lab Med. 2010;48(6):757-67.

11. Vasconcelos E, Fernanda H, Salla R. Role of interleukin-6 and interleukin-15 in exercise. MOJ Immunol. 2018;6(1):17-9.

12. Velders M, Diel P. How Sex Hormones Promote Skeletal Muscle Regeneration. Sports Medicine. 2013;43(11):1089-100.

13. Tiidus PM. Can oestrogen influence skeletal muscle damage, inflammation, and repair? British journal of sports medicine. 2005;39(5):251-3.

14. Oosthuyse T, Bosch AN. The effect of the menstrual cycle on exercise metabolism: implications for exercise performance in eumenorrhoeic women. Sports Med. 2010;40(3):207-27.

15. Hackney AC, Kallman AL, Ağgön E. Female sex hormones and the recovery from exercise: Menstrual cycle phase affects responses. Biomed Hum Kinet. 2019;11(1):87-9.

16. Markofski MM, Braun WA. Influence of menstrual cycle on indices of contraction-induced muscle damage. J Strength Cond Res. 2014;28(9):2649-56.

17. Nosaka K, Clarkson PM. Variability in serum creatine kinase response after eccentric exercise of the elbow flexors. Int J Sports Med. 1996;17(2):120-7.

18. Romero-Parra N, Barba-Moreno L, Rael B, Alfaro-Magallanes VM, Cupeiro R, Díaz ÁE, et al. Influence of the Menstrual Cycle on Blood Markers of Muscle Damage and Inflammation Following Eccentric Exercise. Int J Environ Res Public Health. 2020;17(5):1618.

19. Chaffin ME, Berg KE, Meendering JR, Llewellyn TL, French JA, Davis JE. Interleukin-6 and delayed onset muscle soreness do not vary during the menstrual cycle. Res Q Exerc Sport. 2011;82(4):693-701.

20. Graja A, Kacem M, Hammouda O, Borji R, Bouzid MA, Souissi N, et al. Physical, Biochemical, and Neuromuscular Responses to Repeated Sprint Exercise in Eumenorrheic Female Handball Players: Effect of Menstrual Cycle Phases. The Journal of Strength & Conditioning Research. 9000;Publish Ahead of Print.

21. Kłapcińska B, Sadowska-Krepa E, Manowska B, Pilis W, Sobczak A, Danch A. Effects of a low carbohydrate diet and graded exercise during the follicular and luteal phases on the blood antioxidant status in healthy women. Eur J Appl Physiol. 2002;87(4-5):373-80.

22. McKinley-Barnard SK, Andre TL, Gann JJ, Hwang PS, Willoughby DS. Effectiveness of Fish Oil Supplementation in Attenuating Exercise-Induced Muscle Damage in Women During Midfollicular and Midluteal Menstrual Phases. J Strength Cond Res. 2018;32(6):1601-12.

23. Romero-Parra N, Alfaro-Magallanes VM, Rael B, Cupeiro R, Rojo-Tirado MA, Benito PJ, et al. Indirect Markers of Muscle Damage Throughout the Menstrual Cycle. Int J Sports Physiol Perform. 2020;16(2):190-8.

24. Williams T, Walz E, Lane AR, Pebole M, Hackney AC. The effect of estrogen on muscle damage biomarkers following prolonged aerobic exercise in eumenorrheic women. Biol Sport. 2015;32(3):193-8.

25. Romero-Parra N, Cupeiro R, Alfaro-Magallanes VM, Rael B, Rubio-Arias JÁ, Peinado AB, et al. Exercise-Induced Muscle Damage During the Menstrual Cycle: A Systematic Review and Meta-Analysis. The Journal of Strength & Conditioning Research. 2021;35(2).

26. Hody S, Croisier J-L, Bury T, Rogister B, Leprince P. Eccentric Muscle Contractions: Risks and Benefits. Frontiers in physiology. 2019;10:536-.

27. Cleary MA, Kimura IF, Sitler MR, Kendrick ZV. Temporal pattern of the repeated bout effect of eccentric exercise on delayed onset muscle soreness. Journal of Athletic Training. 2002;37(1):32-6.

28. Howatson G, Van Someren K, Hortobágyi T. Repeated bout effect after maximal eccentric exercise. Int J Sports Med. 2007;28(7):557-63.

29. Howatson G, van Someren KA. Evidence of a contralateral repeated bout effect after maximal eccentric contractions. European Journal of Applied Physiology. 2007;101(2):207-14.

30. Nosaka K, Newton M, Sacco P. Delayed-onset muscle soreness does not reflect the magnitude of eccentric exercise-induced muscle damage. Scandinavian Journal of Medicine & Science in Sports. 2002;12(6):337-46.

31. Elliott-Sale KJ, Minahan CL, de Jonge X, Ackerman KE, Sipilä S, Constantini NW, et al. Methodological Considerations for Studies in Sport and Exercise Science with Women as Participants: A Working Guide for Standards of Practice for Research on Women. Sports Med. 2021;51(5):843-61.

