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Differences in Response to Creatine Supplementation in Women Depending on the Menstrual Cycle Phase: A Narrative Review

Wiktoria Myślicka

https://orcid.org/0009-0005-5209-6504

vika.myslitskaya01@gmail.com

Medical University of Warsaw, Żwirki i Wigury 61, 02-091 Warsaw, Poland

Valery Veyeunik

https://orcid.org/0009-0007-0364-0037

Veevnik224@gmail.com

Medical University of Silesia, Józefa Poniatowskiego 15, 40-055 Katowice, Poland

Agata Chrobak
https://orcid.org/0009-0004-3370-5290
a.chrobakk@gmail.com
Medical University of Warsaw
Żwirki i Wigury 61, 02-091 Warsaw, Poland

Ewa Kacynel
https://orcid.org/0009-0002-8290-9818
evakatsynel@gmail.com
Medical University of Warsaw
Żwirki i Wigury 61, 02-091 Warsaw, Poland

Lizaveta Zhukaya
https://orcid.org/0009-0007-8328-2232
zhukavalizaveta@gmail.com
Medical University of Warsaw
Żwirki i Wigury 61, 02-091 Warsaw, Poland

Darya Volkava
https://orcid.org/0009-0009-2811-146X
darjawolkawa@gmail.com
Medical University of Warsaw
Żwirki i Wigury 61, 02-091 Warsaw, Poland

Volha Sakovich
https://orcid.org/0009-0009-1768-1512
sakovich.olka@gmail.com
Medical University of Warsaw
Żwirki i Wigury 61, 02-091 Warsaw, Poland

Abdulrahman Alansi
https://orcid.org/0000-0001-6544-2916
abodialansi@gmail.com
Medical University of Warsaw
Żwirki i Wigury 61, 02-091 Warsaw, Poland

Kai-Chiun Weng
https://orcid.org/0009-0006-5519-537X
a0939303669@gmail.com
Medical University of Warsaw
Żwirki i Wigury 61, 02-091 Warsaw, Poland

Kateryna Bessmylna
https://orcid.org/0009-0009-9220-9162
kateryna.bessmylna@gmail.com
Medical University of Warsaw
Żwirki i Wigury 61, 02-091 Warsaw, Poland

Alesia Kravets
https://orcid.org/0009-0003-2532-4458
alesiakravets.a@gmail.com
Medical University of Warsaw
Żwirki i Wigury 61, 02-091 Warsaw, Poland

Corresponding Author

Wiktoria Myślicka, vika.myslitskaya01@gmail.com

Abstract

Background. Creatine monohydrate is a widely used ergogenic supplement not subject to the rigorous pharmaceutical standardization or regulatory requirements applied to medicinal products. The majority of research has been conducted in male populations, limiting the validity of direct extrapolation to women. Women have inherently lower creatine stores, and cyclical fluctuations in estradiol and progesterone modulate endogenous creatine synthesis and post-exercise recovery - a domain insufficiently explored in the literature.

Aim. To synthesize available evidence on the influence of menstrual cycle phase on women's response to creatine supplementation, encompassing physical performance, recovery, and mood.

Materials and methods. A literature search was conducted using PubMed, Scopus, and Google Scholar. Data from meta-analyses, systematic reviews, observational studies, and RCTs on creatine metabolism and female physiology were synthesized.

Results. Women exhibit lower endogenous creatine stores and distinct creatine kinase kinetics compared to men. The luteal phase is associated with increased protein catabolism, reduced exercise tolerance, and impaired recovery. Creatine supplementation reduces the fatigue index during the luteal phase and demonstrates potential for mood improvement during the premenstrual phase.

Conclusion. The available evidence suggests that the luteal phase may represent a period of increased creatine demand, during which creatine supplementation could potentially provide greater performance and recovery benefits in women. However, dedicated randomized controlled trials are required to confirm this hypothesis.

Keywords: Creatine Supplementation, Menstrual Cycle, Luteal Phase, Follicular Phase, Female Physiology, Exercise Performance, Dietary Supplement

1. Introduction

Creatine monohydrate (CrM) is one of the most extensively researched and commercially available ergogenic supplements worldwide. Its primary mechanism of action involves augmenting intramuscular phosphocreatine (PCr) stores, thereby accelerating ATP resynthesis during high-intensity, short-duration exercise.[1] Decades of research have consistently demonstrated improvements in anaerobic performance, maximal strength, and post-exercise recovery.[1] Nevertheless, creatine - like the vast majority of dietary supplements - is not subject to the rigorous evaluation required for pharmaceutical registration, resulting in variability in product purity and manufacturing standards across commercial preparations.[2] Women have been systematically underrepresented in sports nutrition research, with menstrual cycle hormonal variability frequently treated as a methodological confound rather than a scientifically meaningful variable.[3] Clinical guidelines derived from male-dominated trials are routinely extrapolated to female populations without biological justification.[3] Women exhibit approximately 70–80% lower rates of endogenous creatine synthesis than men, and the expression of AGAT - the rate-limiting enzyme of creatine synthesis - is directly suppressed by estrogen.[4] Creatine kinase (CK) activity also fluctuates in alignment with estrogen concentrations throughout the menstrual cycle.[5] The luteal phase - defined by concurrent elevations in estradiol and progesterone - is associated with increased protein catabolism, extracellular fluid shifts, and measurable declines in exercise performance.[6,7] This suggests that the luteal phase may represent a period of increased creatine demand, during which supplementation could potentially yield greater ergogenic benefits. However, direct evidence remains limited.

This hypothesis is supported by a randomized crossover trial demonstrating a significant phase × supplement interaction for fatigue index during repeated sprint cycling, with the greatest improvement observed in the luteal phase among women receiving CrM vs. placebo ($p = 0.048$).[8] Beyond physical performance, creatine augmentation of escitalopram at 5 g/day produced a remission rate twice that of placebo at 8 weeks in women with major depressive disorder (52% vs. 26%).[9] Available studies are, however, characterized by significant methodological limitations: small sample sizes, heterogeneity in menstrual cycle phase verification methods, lack of creatine preparation standardization, and difficulty in objectively measuring subjective mood and well-being outcomes. Despite a growing body of evidence, no

review has yet synthesized the available data with menstrual cycle phase as the primary modulating variable of the response to creatine supplementation.[3]

Research Objective. The aim of this narrative review is to synthesize the available scientific evidence on the influence of menstrual cycle phase on women's response to creatine monohydrate supplementation, with particular emphasis on physical performance, post-exercise recovery, and mood. To date, research has focused almost exclusively on male populations, and the few studies including women have rarely treated menstrual cycle phase as a key variable modulating supplementation outcomes. Based on an analysis of biological mechanisms - including the influence of estradiol and progesterone on creatine synthesis, creatine kinase activity, and fluid balance - as well as available clinical data, we postulate that the luteal phase may represent a period of increased creatine demand, during which supplementation could potentially yield greater ergogenic and health benefits in women.

2. Research materials and methods

2.1 Search Strategy and Selection Criteria

In order to conduct this narrative review, a comprehensive literature search was performed using primary scientific databases, including PubMed, Scopus, and Google Scholar. The search targeted peer-reviewed articles published predominantly between 2000 and 2026 to ensure the inclusion of the most contemporary data on female physiology, creatine metabolism, and sports medicine. Clinical guidelines, systematic reviews, meta-analyses, observational studies, randomized controlled trials (RCTs), and experimental studies were included. Keywords and MeSH terms utilized in the search strategy included: *creatine supplementation*, *menstrual cycle*, *follicular phase*, *luteal phase*, *female physiology*, *creatine kinase*, *estrogen*, *exercise performance women*, and *mood women creatine*. Articles not published in English, as well as single case reports lacking a broader population context, were excluded from the synthesis.

2.2 AI.

AI was utilized for linguistic refinement of the manuscript, including translation support and ensuring adherence to academic English writing standards. It is important to emphasize that AI

tools were used strictly as assistive instruments under human supervision. The conception of the review, critical analysis of the literature, formulation of the clinical hypothesis, and final conclusions were exclusively generated and determined by the human authors.

3. Research results

3.1. Biological Mechanisms: Why Menstrual Cycle Phase Should Modulate the Response to Creatine Supplementation

Understanding why menstrual cycle phase may influence the ergogenic response to creatine supplementation requires first establishing the biological foundations of sex-specific creatine metabolism. Creatine is endogenously synthesized via a two-step enzymatic process in which arginine-glycine amidinotransferase (AGAT) serves as the rate-limiting enzyme. Animal model studies have consistently demonstrated that AGAT expression is directly suppressed by estrogen and upregulated by testosterone.[3] This finding carries profound implications for women: because estradiol concentrations fluctuate substantially across the menstrual cycle - rising during the follicular phase, peaking at ovulation, and subsequently declining through the luteal phase - women may experience cyclical variations in endogenous creatine synthetic capacity that have no parallel in male physiology. Paradoxically, although the follicular phase is characterized by higher estradiol and therefore greater AGAT suppression, the luteal phase creates a net state of greater creatine demand through progesterone-driven protein catabolism, impaired glycogen storage, and extracellular fluid shifts - independent of, and superimposed upon, the hormonal modulation of AGAT activity.

Creatine kinase (CK) activity - the central enzyme of the phosphocreatine/ATP buffering system - also fluctuates in synchrony with estrogen concentrations throughout the menstrual cycle, with the lowest values observed during the follicular phase and further decreases noted with advancing age and during pregnancy.[5] Estrogen's well-documented membrane-stabilizing and antioxidant properties provide an additional layer of modulation: during the follicular phase, elevated estrogen reduces sarcolemmal permeability and attenuates post-exercise CK leakage, conferring a degree of muscular protection that is progressively withdrawn as estrogen falls in the late luteal phase.[10] This withdrawal effect is particularly relevant in a sports context,

where the capacity for rapid muscle recovery between training sessions is a primary determinant of training adaptation.

The luteal phase creates a constellation of physiological conditions that converge to increase creatine demand. Elevated progesterone antagonizes the anabolic effects of estrogen on skeletal muscle, promoting protein catabolism and impairing glycogen storage.[6] Concurrently, progesterone-mediated extracellular fluid shifts reduce intracellular hydration, potentially impairing cellular creatine uptake and phosphocreatine buffering capacity. Core body temperature rises by 0.3–0.5°C, increasing thermoregulatory demands during exercise and accelerating the onset of fatigue.[6] Taken together, these changes produce a physiological environment in which the energetic demands of exercise are elevated, the capacity for phosphocreatine buffering may be reduced, and recovery is impaired - precisely the conditions under which exogenous creatine supplementation would be expected to yield the greatest ergogenic benefit. This biological convergence forms the mechanistic foundation for the first hypothesis advanced by this review: the luteal phase may represent a period of elevated creatine demand and therefore a potential window of enhanced benefit from creatine supplementation, warranting investigation of phase-targeted intensification protocols.

3.2. Clinical Evidence: Creatine Supplementation Across Menstrual Cycle Phases

Despite the compelling mechanistic rationale outlined above, the clinical evidence base for phase-specific effects of creatine supplementation remains remarkably limited. All available phase-specific trials have been conducted by a single research group at the University of North Carolina at Chapel Hill, and all have employed short-term creatine loading protocols (4×5 g/day for 5 days) rather than chronic supplementation strategies. This concentration of evidence in a single laboratory underscores the need for independent replication.

The landmark trial by Gordon et al. (2023) was the first to directly evaluate phase-specific effects of creatine loading on exercise performance in women.[8] In this randomized, double-blind, crossover study involving 39 active women, participants underwent testing in both the follicular (low-hormone) and luteal (high-hormone) phases following loading with either creatine monohydrate (20 g/day) or non-caloric placebo. The primary exercise outcome was a repeated sprint cycling test (10 × 6-second maximal sprints with 60-second recovery) - a

protocol specifically designed to tax the phosphocreatine energy system and directly relevant to sports science. A statistically significant phase × supplement interaction was observed for the fatigue index ($p = 0.048$), with the creatine group demonstrating a mean improvement of $-5.8 \pm 19.0\%$ in the luteal phase compared to $+0.1 \pm 8.1\%$ in the placebo group. Critically, both groups showed reduced sprint performance in the luteal phase - confirming the performance-decreasing effect of the high-hormone environment - but only the creatine group showed a partial attenuation of this decrement. Heart rate variability (HRV) was not significantly influenced by creatine in either phase.[8]

A meta-analysis of exercise performance across menstrual cycle phases found that aerobic performance is generally superior during the follicular phase, while maximal strength tends to reach its lowest values during the mid-luteal phase.[11] However, the scientific literature is not without controversy: a rigorous investigation using stable isotope methodology in 12 young women found no significant differences in myofibrillar protein synthesis (follicular: $1.52 \pm 0.27\%$/day; luteal: $1.46 \pm 0.25\%$/day in exercised legs) or protein breakdown between phases in response to six days of resistance exercise.[12] A systematic review similarly concluded that menstrual cycle phase exerts a trivial effect on maximal voluntary contraction force and explosive strength, with Hedges' g values below 0.15.[13] These conflicting findings underscore the profound methodological heterogeneity in this field and highlight the urgent need for standardized research protocols - particularly in phase verification methods.

Moore et al. (2025) extended the work of Gordon et al. by examining cellular-level outcomes following the same creatine loading protocol in 20 moderately active women.[14] Phase angle (PhA), a validated non-invasive marker of cellular membrane integrity and intracellular hydration, was significantly higher in the creatine group during the luteal phase compared to placebo, suggesting creatine may partially counteract progesterone-mediated extracellular fluid shifts. Countermovement jump (CMJ) height showed a trend toward preservation in the creatine group during the luteal phase, though the small sample size precluded statistical significance.[14]

Moore et al. (2023) examined fluid distribution following creatine loading in 30 women stratified as naturally menstruating (NM) or using hormonal contraceptives (HC).[15] No significant changes in TBW, ECF, or ICF were observed across either phase or hormonal group. The absence of the classic body mass gain associated with creatine loading in males reflects

sex-specific differences in creatine-induced fluid dynamics. The inclusion of HC users as a separate subgroup revealed qualitatively different responses to creatine loading - a finding central to the second hypothesis of this review.[15]

A separate trial demonstrated that daily creatine supplementation (5 g/day for 6 weeks) improved total sleep duration on resistance training days in naturally menstruating women.[16] Given that sleep architecture is disrupted during the luteal phase due to progesterone-mediated increases in core body temperature, this finding has direct relevance for athletic recovery optimization. Epidemiological evidence from the NHANES 2017–2020 cohort (n = 4,522 women) further supports the clinical importance of adequate creatine availability: women consuming suboptimal dietary creatine (<13 mg/kg/day) had significantly higher risks of pelvic infection (OR = 1.68), hysterectomy (OR = 1.42), and oophorectomy (OR = 1.54); the relationship between suboptimal creatine intake and menstrual irregularity (including oligomenorrhea) also reached statistical significance ($p < 0.001$).[17] Because of the observational nature of the study, these associations should not be interpreted as evidence of causality.

In the sports context, women athletes' elevated creatine demands from training may further deplete endogenous reserves and increase vulnerability to cycle-related health disruptions. A meta-analysis of 10 RCTs in 211 older women confirmed that creatine combined with resistance training significantly improved upper-body strength ($p = 0.04$) and both upper- and lower-body strength in studies ≥24 weeks ($p = 0.03–0.05$), establishing the robust ergogenic efficacy of creatine in women as a foundation for phase-specific investigations.[18]

Table 1. Summary of clinical studies on creatine supplementation in women with relevance to menstrual cycle phase.

Author / Year	Design	Sample	Intervention & Outcome Measures	Phase Verification	Key Results	Limitations / Notes
Gordon et al. (2023) [8]	RCT, double-blind, crossover	n = 39 active women	CrM 20 g/day × 5 days vs. placebo; 10 × 6-s sprint cycling test	BBT + cycle tracking app (follicular & luteal)	Significant phase × supplement interaction for fatigue index ($p = 0.048$); creatine group: −5.8 ± 19.0% in luteal phase vs. +0.1 ± 8.1% placebo. HRV: ns.	First phase-specific RCT; All trials from UNC Chapel Hill
Moore et al. (2025) [14]	RCT, crossover	n = 20 moderately active women	CrM 20 g/day × 5 days vs. placebo; Phase angle (PhA), CMJ height	Serum hormone confirmation (follicular & luteal)	PhA significantly higher in creatine group during luteal phase vs.	Cellular integrity marker; Small sample limits power

					placebo ($p < 0.05$). CMJ: trend toward preservation in luteal phase (ns - underpowered).	
Moore et al. (2023) [15]	RCT, controlled	n = 30 women (NM vs. HC subgroups)	CrM 20 g/day × 5 days vs. placebo; TBW, ECF, ICF (bioimpedance)	Cycle phase + hormonal contraceptive status stratified	No significant changes in TBW, ECF, or ICF in either group or phase. HC users showed qualitatively different fluid responses vs. NM women.	Absence of classic body mass gain seen in men; First HC stratification in creatine trial
Aguiar Bonfim Cruz et al. (2024) [16]	RCT, controlled	n = NM women (sample size NR)	CrM 5 g/day × 6 weeks vs. placebo; Sleep duration (actigraphy)	Naturally menstruating (phases not separately analysed)	Creatine significantly improved total sleep duration on resistance training days vs. non-training days. Effect relevant to luteal phase recovery disruption.	Indirect relevance to luteal phase; Sleep architecture not fully reported

Avon et al. (2025) [19]	Controlled trial	n = 11 female recreational athletes	Loading (20 g/day) vs. maintenance (5 g/day) × 14 days; Body composition, fluid distribution	Menstrual cycle phase not controlled	Both strategies produced measurable body composition changes. No pronounced body mass gain (unlike males). Sex-specific fluid dynamics confirmed.	Strategy comparison study; No phase control - significant limitation
Lyoo et al. (2012) [9]	RCT, double-blind, placebo-controlled	n = 52 women with MDD	CrM 5 g/day augmenting escitalopram × 8 weeks vs. placebo + SSRI	Not applicable (psychiatric trial)	Remission rate: 52% (creatine) vs. 26% (placebo) at 8 weeks. OR ≈ 3.1; bioenergetic pathway implicated in mood modulation.	Mood/psychiatric endpoint; Not an exercise trial; women only
Santos et al. (2021) [18] [meta-analysis]	Systematic review & meta-analysis (10 RCTs)	n = 211 older females	Creatine + resistance training vs. placebo + RT; Upper/lower body strength	Menstrual cycle phase not applicable (postmenopausal/older)	Creatine + RT significantly improved upper-body strength ($p = 0.04$) and both upper/lower strength in	Foundation evidence for female ergogenic efficacy; Older cohort - not directly phase-applicable

					studies ≥24 weeks (p = 0.03–0.05).	
Ostojic et al. (2024) [17] [NHANES]	Cross-sectional epidemiological (NHANES 2017–2020)	n = 4,522 women	Dietary creatine intake (<13 mg/kg/day) vs. adequate; Reproductive health outcomes	Not applicable (population cohort)	Suboptimal intake associated with significantly higher odds of pelvic infection (OR 1.68), hysterectomy (OR 1.42), oophorectomy (OR 1.54). Oligomenorrhea: see note.	Observational - causality not established; dietary creatine-oligomenorrhea link significant (p < 0.001) but mechanism not established

Abbreviations: CrM = creatine monohydrate; RCT = randomised controlled trial; NM = naturally menstruating; HC = hormonal contraceptive users; TBW = total body water; ECF = extracellular fluid; ICF = intracellular fluid; CMJ = countermovement jump; PhA = phase angle; HRV = heart rate variability; MDD = major depressive disorder; SSRI = selective serotonin reuptake inhibitor; NR = not reported; ns = not significant; RT = resistance training.

3.3. Inter-Individual Hormonal Variability: A Critical and Underappreciated Confounder

The second central hypothesis of this review emerges from a consistent observation: the hormonal environment of women is not a uniform, predictable variable but a highly individualized biological system. Cycle length, hormonal magnitude, and physiological consequences vary substantially between individuals, with profound implications for how creatine supplementation research in women should be designed and translated into sports nutrition practice.

Phase verification methodology represents the most immediate source of research heterogeneity. In the Gordon et al. (2023) trial, BBT combined with a tracking application was used; in Moore et al. (2025), serum hormone confirmation was employed.[8,14] These methodological differences create uncertainty about whether "luteal phase" testing across different studies corresponds to equivalent hormonal environments. The systematic review showing trivial phase effects on strength[13] and the null MPS findings[12] may reflect genuine biological equivalence - or statistical dilution of real effects by high inter-individual variability in hormonal amplitude and timing. Women with attenuated estradiol peaks, shortened luteal phases, or subclinical luteal phase deficiency may respond very differently to phase-targeted supplementation than women with robust hormonal profiles.

The inclusion of hormonal contraceptive (HC) users in creatine research introduces a qualitatively different hormonal environment. In the Moore et al. (2023) fluid distribution trial, HC users showed different responses to creatine loading than naturally menstruating women.[15] Combined oral contraceptives suppress natural estradiol and progesterone cycles, replacing them with synthetic progestins and ethinyl estradiol at pharmacologically stable concentrations. In a sports nutrition context, this is practically significant: a substantial proportion of women athletes use hormonal contraception, and protocols developed in naturally cycling women may not translate directly to this population. Conversely, research conducted primarily in HC users may underestimate phase-specific variation in naturally cycling athletes.

Individual differences in baseline creatine stores add another layer of variability. Women with lower baseline intramuscular creatine concentrations - vegetarians, vegans, or individuals with

low dietary protein intake - may respond more dramatically to supplementation regardless of cycle phase, as their creatine system operates further below saturation.[3] In sports populations, dietary patterns vary enormously between disciplines, adding a nutrition-specific confound to the hormonal variability already described.

A recent supplementation strategy study comparing loading (20 g/day) versus maintenance (5 g/day) protocols in 11 female recreational athletes over 14 days found that both strategies produced measurable body composition changes without the pronounced body mass gain seen in males.[19] This reinforces the sex-specific nature of creatine's fluid dynamics and further supports the need for women-specific supplementation protocols. A comprehensive review covering the full female lifespan confirmed that early studies documenting performance benefits in women frequently failed to account for menstrual cycle variability and called for future research to systematically incorporate hormonal phase verification.[3] Smith-Ryan et al. (2025) further emphasised that creatine research across the female lifespan — from menstruation through pregnancy to menopause — consistently lacks hormonal phase control, underscoring the need for cycle-integrated supplementation protocols.[20]

Age-related hormonal changes introduce additional complexity. Perimenopausal women experience irregular cycles with declining estrogen and progesterone. A 2025 trial found that creatine supplementation combined with resistance training improved lower-body strength and sleep quality in perimenopausal participants, suggesting preserved responsiveness even in a hormonally disrupted environment.[22] Women with PMS or PMDD - affecting approximately 47.8% of reproductive-age women[21] - represent hormonal phenotypes with amplified neurobiological sensitivity to the luteal phase milieu and may constitute a subpopulation for whom phase-targeted creatine supplementation could yield disproportionate benefits, both ergogenic and mood-related. A landmark RCT demonstrated that creatine augmentation of SSRI therapy in women with MDD produced remission rates twice those of placebo (52% vs. 26%), implicating the bioenergetic pathway as a relevant mechanism for mood modulation in women.[9] The convergence of all these sources of variability forms the foundation of the second hypothesis: a one-size-fits-all supplementation protocol is insufficient for women, and future research must account for individual hormonal profiles to generate clinically meaningful, personalized recommendations. In elite sport, where marginal gains are decisive, this failure to

account for individual hormonal variability may represent a significant missed opportunity for performance optimization in women athletes.

Finally, a dose-ranging ^{31}P-MRS study in adolescent girls with SSRI-resistant depression confirmed that creatine supplementation at 2, 4, and 10 g/day for 8 weeks produced dose-dependent increases in brain phosphocreatine concentrations correlating with clinical improvement,[23] while an open-label pilot study in 15 adult women with SSRI/SNRI-resistant depression found that combination augmentation with creatine and 5-HTP reduced HAM-D scores by 60% over 8 weeks.[24] These findings, while not phase-specific, highlight creatine's mood-relevant mechanisms in women and reinforce the relevance of the bioenergetic pathway to both physical and psychological aspects of luteal phase vulnerability.

4. Discussion

4.1. The Luteal Phase as a Window of Elevated Creatine Demand: Clinical and Practical Implications

An analysis of the available literature suggests that the luteal phase of the menstrual cycle may create a constellation of physiological conditions that converge to increase creatine demand in women, although the clinical evidence base supporting this hypothesis remains limited and requires independent replication. The estrogen-driven suppression of AGAT-dependent endogenous creatine synthesis, progesterone-mediated protein catabolism, impaired glycogen storage, extracellular fluid shifts, and elevated core body temperature collectively produce a biological environment in which the phosphocreatine buffering system operates under heightened demand precisely when its endogenous supply may be most compromised.[3,6] This mechanistic framework is directly supported by the available clinical data. Gordon et al. (2023) demonstrated a statistically significant phase × supplement interaction for fatigue index during repeated sprint cycling ($p = 0.048$), with the creatine group showing a mean improvement of $-5.8 \pm 19.0\%$ during the luteal phase compared to $+0.1 \pm 8.1\%$ in the placebo group.[8] Moore et al. (2025) extended these findings by demonstrating preserved cellular integrity - measured via phase angle - specifically during the luteal phase in the creatine group, suggesting that creatine may partially counteract progesterone-mediated intracellular fluid loss.[14] These findings represent the first direct clinical evidence that the ergogenic response to creatine

supplementation in women is not phase-invariant but is modulated by the hormonal milieu of the menstrual cycle.

The practical implications for sports nutrition are considerable. The performance outcomes showing the clearest phase-specific creatine benefit - fatigue index during repeated sprints and explosive power indices - are directly relevant to athletes in team sports, sprint disciplines, and strength sports.[8,14] Sports nutrition practitioners should therefore consider the luteal phase as a period warranting particular attention to creatine status in women athletes. The most pressing and as-yet unanswered clinical question is whether proactively intensifying creatine intake in the days preceding or during the luteal phase - rather than maintaining a constant supplementation dose throughout the cycle - amplifies these benefits. This concept of phase-targeted dosing periodization represents a novel and clinically meaningful research direction. Until dedicated trials address this question, a pragmatic recommendation for practitioners is to ensure that women athletes maintain consistent daily creatine supplementation (3–5 g/day) throughout the cycle, with particular attention to compliance during the luteal phase, when ergogenic requirements may be increased and - as suggested by the sleep data of Aguiar Bonfim Cruz et al. (2024)[16] - recovery quality may also be most vulnerable.

It should be noted, however, that the available evidence base carries important limitations that constrain the strength of these recommendations. All phase-specific creatine trials to date have employed short-term loading protocols from a single research group, limiting both the duration of ergogenic assessment and the generalizability of findings across different athlete populations, disciplines, and geographical settings. The measurement of exercise performance across menstrual cycle phases presents inherent methodological challenges: standardizing testing conditions for variation in thermoregulatory responses, perceived exertion, motivation, and sleep quality across phases requires rigorous phase verification and controlled environments that remain difficult to implement in applied sport settings. Furthermore, as with all dietary supplements, the absence of pharmaceutical-grade standardization introduces variability in creatine product quality that may contribute to inconsistencies across studies and limit the reliability of findings for real-world practice.

4.2. Inter-Individual Hormonal Variability: Toward Personalized Supplementation in Women Athletes

The second and equally important conclusion emerging from this review is that the biological heterogeneity of women's hormonal profiles fundamentally precludes the application of uniform, phase-averaged creatine supplementation protocols across female athletic populations. The wide spectrum of cycle lengths, hormonal amplitudes, luteal phase durations, and ovulatory patterns among women means that group-level phase data may systematically obscure the very effects that phase-specific strategies seek to exploit. The systematic review by Colenso-Semple et al. (2023), finding trivial phase effects on maximal strength,[13] and the isotope methodology study finding no differences in muscle protein synthesis between phases[12] do not necessarily contradict the phase-specific benefits observed in creatine loading trials. Rather, they may reflect the statistical dilution of real hormonal effects by the wide spectrum of hormonal profiles among study participants - an interpretation consistent with the second hypothesis of this review.

The qualitatively different responses to creatine loading observed between naturally menstruating women and hormonal contraceptive users in the Moore et al. (2023) fluid distribution trial[15] provide direct empirical support for this hypothesis. Combined oral contraceptives suppress natural estradiol and progesterone cycles, replacing them with synthetic progestins and ethinyl estradiol at pharmacologically stable concentrations - a fundamentally different hormonal context from the dynamic natural cycle. Given that a substantial proportion of women athletes use hormonal contraception, protocols developed exclusively in naturally cycling women may not translate directly to this population, and vice versa. This has immediate practical consequences: sports nutrition practitioners must ascertain hormonal contraceptive status before implementing cycle-based creatine protocols, and researchers must stratify by this variable as a standard design feature.

Individual differences in baseline creatine stores further compound this variability. Women athletes following vegetarian or vegan dietary patterns - increasingly common across endurance and aesthetic sports - may have substantially lower baseline intramuscular creatine concentrations and therefore respond more dramatically to supplementation regardless of cycle phase.[3] Conversely, athletes with habitually high dietary creatine intakes may show blunted responses due to closer proximity to intramuscular saturation. In elite sport, where individual monitoring of hormonal status is increasingly feasible through wearable technology and point-of-care hormone testing, there is a compelling case for integrating menstrual cycle tracking into

creatine supplementation planning - not as a fixed schedule applied uniformly to all athletes, but as an individualized tool for identifying each athlete's unique window of greatest creatine responsiveness. This approach aligns with the broader trend toward precision nutrition in elite sport and represents a logical next step in the translation of the mechanistic evidence reviewed here into applied practice.

4.3. Limitations

While this review synthesizes emerging evidence to propose a novel framework for cycle-informed creatine supplementation in women athletes, several limitations must be acknowledged.

First, as a narrative review, this manuscript does not employ the exhaustive, protocol-driven search strategies and quantitative data synthesis characteristic of systematic reviews or meta-analyses. Consequently, the selection of literature is inherently susceptible to selection bias, and the conclusions drawn should be interpreted as hypothesis-generating rather than definitive.

Second, and critically, creatine used across all studies included in this review was classified as a dietary supplement rather than a medicinal product. As such, it was not subject to the rigorous preclinical and clinical evaluation, standardized manufacturing processes, or regulatory approval requirements applied to pharmaceutical drugs. This distinction carries meaningful consequences for the interpretation of available findings: variability in product purity, bioavailability, and manufacturing standards across commercial creatine preparations may contribute to inconsistencies observed between studies and limits the precision with which dosing recommendations can be formulated. Until creatine preparations used in research are standardized to pharmaceutical-grade specifications, the translatability of trial findings to real-world supplementation practice remains constrained.

Third, the evidence base for phase-specific effects of creatine supplementation is confined to a small number of trials conducted by a single research group, all employing short-term loading protocols of five days duration. The absence of independent replication, longer supplementation periods, and chronic phase-aligned supplementation protocols substantially limits the strength of conclusions that can be drawn regarding the optimal dosing strategy, the durability of phase-

specific effects, and the cumulative benefits of luteal phase-targeted supplementation over a training season.

Fourth, the literature on menstrual cycle effects on exercise performance is characterized by profound methodological heterogeneity, particularly in the methods used to verify menstrual cycle phase. Calendar-based phase estimation, basal body temperature monitoring, urinary LH surge detection, and serum hormone assays represent fundamentally different levels of precision, and their inconsistent application across studies creates substantial uncertainty about whether "luteal phase" testing in different trials corresponds to equivalent hormonal environments. This heterogeneity limits cross-study comparability and may explain the divergent findings observed in the broader literature.

Fifth, the role of hormonal contraceptives - used by a substantial proportion of women athletes worldwide - in modulating the response to creatine supplementation remains poorly understood. Available evidence suggests that naturally menstruating women and hormonal contraceptive users may respond differently to creatine loading,[15] yet the majority of published research has either excluded HC users or failed to stratify analyses by hormonal status. This represents a critical gap given the prevalence of hormonal contraceptive use in competitive sport.

Sixth, the extrapolation of mechanistic evidence - much of which derives from animal models demonstrating estrogen-mediated suppression of AGAT expression - to the complex, cyclically varying hormonal environment of human women requires caution. The direct human evidence for cycle-dependent fluctuations in endogenous creatine synthesis remains limited, and the degree to which AGAT suppression during the follicular phase translates into clinically meaningful reductions in intramuscular creatine availability has not been directly quantified in humans.

Finally, individual differences in baseline creatine stores, dietary creatine intake, training status, body composition, and genetic variation in creatine transporter expression introduce substantial inter-individual variability that aggregate group-level analyses cannot adequately capture. Future research employing n-of-1 trial designs or individual response analyses will be necessary to characterize the full spectrum of hormonal and nutritional factors determining the magnitude of phase-specific creatine response in women athletes.

5. Conclusions

Based on the analysis of the available literature, the following conclusions can be drawn:

1. The menstrual cycle exerts a significant influence on creatine metabolism in women through cyclical fluctuations in estradiol and progesterone. Estrogen-mediated suppression of AGAT-dependent endogenous creatine synthesis, combined with progesterone-driven protein catabolism and extracellular fluid shifts, creates a dynamic metabolic environment that fundamentally differs from the stable hormonal background in men and limits the validity of direct extrapolation of male-derived supplementation protocols to female populations.
2. Available mechanistic and clinical evidence suggests that the luteal phase may represent a period of increased physiological vulnerability and potentially enhanced responsiveness to creatine supplementation. The statistically significant phase × supplement interaction for fatigue index during repeated sprint cycling ($p = 0.048$), observed exclusively in the luteal phase, constitutes the first direct clinical evidence that women's response to creatine supplementation is modulated by menstrual cycle phase.
3. Whether proactively increasing creatine intake during the luteal phase amplifies ergogenic benefits beyond those achieved with continuous supplementation remains the critical unanswered research question. Future randomized controlled trials should specifically test luteal phase-targeted dosing protocols with rigorous hormonal phase verification, sports-relevant performance outcomes, and independent replication across multiple research groups.
4. The biological heterogeneity of women's hormonal profiles - encompassing cycle length variability, hormonal amplitude, luteal phase duration, ovulatory status, and hormonal contraceptive use - fundamentally precludes the application of uniform supplementation protocols across female athletic populations. Hormonal contraceptive status must be treated as a primary stratification variable in future research, and sports nutrition practitioners must account for individual hormonal profiles when designing creatine supplementation strategies for women athletes.
5. Creatine used across all reviewed studies was classified as a dietary supplement rather than a medicinal product and was therefore not subject to pharmaceutical-grade standardization or regulatory approval. Variability in product purity and manufacturing standards may

contribute to inconsistencies across studies and limits the precision of current dosing recommendations. Pharmaceutical-grade standardization of creatine preparations used in research would substantially improve the comparability and reliability of future findings.

6. Beyond performance, adequate creatine availability appears relevant to reproductive health, sleep quality, and mood regulation in women - domains of particular significance during the luteal and premenstrual phases. The bioenergetic mechanism through which creatine augments antidepressant efficacy in women with MDD may also be relevant to women athletes experiencing luteal phase mood disturbances, reduced motivation, or premenstrual dysphoric symptoms, extending creatine's potential role beyond physical performance to psychological readiness and training consistency.

Disclosure.

The use of AI tools for language refinement has been disclosed in the Materials and Methods section.

Author Contributions:

Conceptualization: W.M., V.V.; Methodology: W.M., L.Z., K.B.; Investigation: W.M., A.A., E.K., D.V., V.S., A.C.; Data Curation: A.K., E.K., K.-C.W.; Writing – original draft: Introduction and Search Strategy: W.M., L.Z.; Biological Mechanisms and Results: W.M., D.V., K.B.; Clinical Evidence and Creatine Supplementation: A.A., K.-C.W., V.V.; Discussion and Conclusions: W.M., V.S., A.C.; Writing – Review & Editing: W.M., V.V., L.Z., K.B., D.V., A.A., E.K., A.K., K.-C.W., V.S., A.C.

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References

1. Kreider RB, Stout JR. Creatine in health and disease. *Nutrients*. 2021;13(2):447. https://doi.org/10.3390/nu13020447
2. Dolan E, Burke R, Mc Goldrick A. Creatine supplementation beyond athletics: benefits of different types of creatine for women, vegans, and clinical populations - a narrative review. *Nutrients*. 2024;17(1):95. https://doi.org/10.3390/nu17010095
3. Smith-Ryan AE, Cabre HE, Eckerson JM, Candow DG. Creatine supplementation in women's health: a lifespan perspective. *Nutrients*. 2021;13(3):877. https://doi.org/10.3390/nu13030877
4. Ellery SJ, Walker DW, Dickinson H. Creatine for women: a review of the relationship between creatine and the reproductive cycle and women-specific benefits of creatine therapy. *Amino Acids*. 2016;48(8):1807–1817. https://doi.org/10.1007/s00726-016-2199-y
5. Thompson HS, Scordilis SP, De Souza MJ. Serum creatine kinase activity varies with ovulatory status in regularly exercising, premenopausal women. *Horm Res*. 2006;65(3):151–158. https://doi.org/10.1159/000091805
6. Wen Y, Gao B, Wang R, Zhao C. Exercise performance at different phases of the menstrual cycle: measurements, differences, and mechanisms - a narrative review. *Front Endocrinol*. 2025;16:1448686. https://doi.org/10.3389/fendo.2025.1448686
7. Pereira HM, Larson RD, Bemben DA. Menstrual cycle effects on exercise-induced fatigability. *Front Physiol*. 2020;11:517. https://doi.org/10.3389/fphys.2020.00517
8. Gordon AN, Moore SR, Patterson ND, Hostetter ME, Cabre HE, Hirsch KR, Hackney AC, Smith-Ryan AE. The effects of creatine monohydrate loading on exercise recovery in active women throughout the menstrual cycle. *Nutrients*. 2023;15(16):3567. https://doi.org/10.3390/nu15163567
9. Lyoo IK, Yoon S, Kim TS, et al. A randomized, double-blind placebo-controlled trial of oral creatine monohydrate augmentation for enhanced response to a selective serotonin reuptake inhibitor in women with major depressive disorder. *Am J Psychiatry*. 2012;169(9):937–945. https://doi.org/10.1176/appi.ajp.2012.12010009

10. Minahan, C., Joyce, S., Bulmer, A.C. *et al.* The influence of estradiol on muscle damage and leg strength after intense eccentric exercise. *Eur J Appl Physiol* **115**, 1493–1500 (2015). https://doi.org/10.1007/s00421-015-3133-9
11. McNulty KL, Elliott-Sale KJ, Dolan E, Swinton PA, Ansdell P, Goodall S, Thomas K, Hicks KM. The effects of menstrual cycle phase on exercise performance in eumenorrheic women: a systematic review and meta-analysis. *Sports Med*. 2020;50(10):1813–1827. https://doi.org/10.1007/s40279-020-01319-3
12. Colenso-Semple LM, McKendry J, Lim C, Atherton PJ, Wilkinson DJ, Smith K, Phillips SM. Menstrual cycle phase does not influence muscle protein synthesis or whole-body myofibrillar proteolysis in response to resistance exercise. *J Physiol*. 2023;603(5):1109–1121. https://doi.org/10.1113/JP287342
13. Colenso-Semple LM, D'Souza AC, Elliott-Sale KJ, Phillips SM. Current evidence shows no influence of women's menstrual cycle phase on acute strength performance or adaptations to resistance exercise training. *Front Sports Act Living*. 2023;5:1054542. https://doi.org/10.3389/fspor.2023.1054542
14. Moore SR, Mutuwa AG, Brown AF, Smith-Ryan AE. The effects of creatine loading on cellular integrity and jump performance across the menstrual cycle. *J Int Soc Sports Nutr*. 2025;22(1):2533651. https://doi.org/10.1080/15502783.2025.2533651
15. Moore SR, Gordon AN, Cabre HE, Hackney AC, Smith-Ryan AE. A randomized controlled trial of changes in fluid distribution across menstrual phases with creatine supplementation. *Nutrients*. 2023;15(2):429. https://doi.org/10.3390/nu15020429
16. Aguiar Bonfim Cruz AJ, Cabre HE, Moore SR, Smith-Ryan AE. Creatine improves total sleep duration following resistance training days versus non-resistance training days among naturally menstruating women. *Nutrients*. 2024;16(16):2772. https://doi.org/10.3390/nu16162772
17. Ostojic SM, Stea TH, Ellery SJ, Smith-Ryan AE. Association between dietary intake of creatine and women reproductive health: Evidence from NHANES 2017–2020. *Food Sci Nutr*. 2024;12(7):4893–4898. https://doi.org/10.1002/fsn3.4135
18. Santos EEP, Araújo RC, Candow DG, et al. Efficacy of creatine supplementation combined with resistance training on muscle strength and muscle mass in older women: a systematic review and meta-analysis. *Nutrients*. 2021;13(11):3757. https://doi.org/10.3390/nu13113757

19. Avon IH, Levers KS, Wasilczyk N, et al. Creatine monohydrate supplementation strategies on body composition and water distribution in female recreational athletes. *J Int Soc Sports Nutr*. 2025;22(1):2533668. https://doi.org/10.1080/15502783.2025.2533668
20. Smith-Ryan AE, DelBiondo GM, Brown AF, Kleiner SM, Tran NT, Ellery SJ. Creatine in women's health: bridging the gap from menstruation through pregnancy to menopause. *J Int Soc Sports Nutr*. 2025;22(1):2502094. https://doi.org/10.1080/15502783.2025.2502094
21. Gudipally PR, Sharma GK. Premenstrual Syndrome. In: *StatPearls*. StatPearls Publishing; 2023. https://www.ncbi.nlm.nih.gov/books/NBK560698/
22. Hall L, Klassen S, Holbein J, Waters J. Impact of creatine supplementation on menopausal women's body composition, cognition, estrogen, strength, and sleep. *J Int Soc Sports Nutr*. 2025;22(1):2533673. https://doi.org/10.1080/15502783.2025.2533673
23. Kondo DG, Forrest LN, Shi X, Sung YH, Hellem TL, Huber RS, Renshaw PF. Creatine target engagement with brain bioenergetics: a dose-ranging phosphorus-31 MRS study of adolescent girls with SSRI-resistant depression. *Amino Acids*. 2016;48(8):1941–1954. https://doi.org/10.1007/s00726-016-2194-3
24. Kious BM, Kondo DG, Renshaw PF. An open-label pilot study of combined augmentation with creatine monohydrate and 5-hydroxytryptophan for SSRI- or SNRI-resistant depression in adult women. *J Clin Psychopharmacol*. 2019;39(4):383–391. https://doi.org/10.1097/jcp.0000000000000754