

Original paper

The effects of menstrual cycle phase on clinical measures of concussion in healthy college-aged females

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Abstract

The management of concussion and mild traumatic brain injury is an area of clinical uncertainty for many sports medicine professionals. While recent studies suggest sex differences in neurocognitive function may exist, our understanding of the effects of menstrual cycle phase and oral contraceptive pill (OCP) use in healthy females is limited. The purpose of this study was to investigate whether there were changes in neurocognitive function, postural stability and self-reported symptoms between the early and late stages of the menstrual cycle, and also to identify whether performance across menstrual cycle would differ between females using OCP and eumenorrheic females not using OCP. Healthy college-aged females completed a standard concussion test battery including computerised assessment of neurocognitive function, postural stability and symptom status. Participants completed the counterbalanced testing design during the early and late phases of their menstrual cycle. No significant main effects or interactions for any neurocognitive function or postural stability outcome measure were observed. Eumenorrheic females endorsed a higher number of symptoms and reported an increased symptom severity score compared to females using OCP. Menstrual cycle phase had no effect on the total severity or the number of symptoms endorsed. These results suggest preseason neurocognitive and postural stability baseline tests are stable across the menstrual cycle, regardless of OCP use. Therefore, decreased performance on these measures following a suspected concussion is likely not attributable to menstrual cycle phase or use of OCP.

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1. Introduction

Concussion remains an area of great interest among sports medicine professionals. It has been estimated that as many as 1.6–3.8 million cases of mild traumatic brain injury occur in sport and recreation each year in the United States.¹ Despite a better understanding of the mechanisms of injury and sequelae of post-concussion symptoms, the management of head injuries involves more clinical uncertainty and controversy than any other area of sports medicine.²

A number of reports have sought to identify sex differences in clinical measures of concussion following injury.^{3,4} Although these studies have provided some insight into

potential sex-related factors pertaining to concussion, they have been inconclusive for the most part. Furthermore, research investigating the effects of menstrual cycle phase and associated hormonal fluctuations on clinical measures of concussion including neuropsychological testing, balance performance and self-reported symptoms, is limited in the literature.

During the menstrual cycle, estradiol and progesterone increase to a greater extent during the luteal (i.e. late, post-ovulatory) phase, compared to the follicular (i.e. early, pre-ovulatory) phase.⁵ Researchers have previously proposed an association between general sports-related injuries in women and the menstrual cycle,^{6,7} with higher rates of general injuries reported during the luteal phase. Understanding the effects of menstrual cycle phase on neurocognitive function is therefore warranted, especially with its potential application to post-injury management of concussion. However, few studies have investigated the effects of the menstrual

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cycle on neurocognition in females.^{8,9} One previous study reported greater postural sway during the mid-luteal phase compared to the early follicular or ovulatory phases, in women experiencing pre-menstrual syndrome.⁵ This is surprising, since earlier studies have suggested females typically excelled in verbal and fine motor abilities during the mid-luteal phase compared with the menstrual phase.^{10,11} Previous reports also suggest no effect of menstrual cycle phase on verbosequential and visuospatial neuropsychological tests.¹² The study of these parameters in the context of a sports-related concussion model is limited and complicated further by athletes, use of oral contraceptive pills (OCP), and cyclical changes in hormones in eumenorrheic females.

The investigation of menstrual cycle phase on neurocognitive function, balance performance and self-reported symptoms is a logical progression so that clinicians may be better equipped to manage injuries in concussed females. For example, if a female completes preseason baseline testing at a phase in her menstrual cycle where she would typically score poorly and is post-injury-tested during another phase of her menstrual cycle during which the score may be increased, the clinician may return an athlete to play prematurely.

The purpose of this study was to investigate whether there were changes in neurocognitive function, postural stability and self-reported symptoms between the follicular (early) and luteal (late) stages of the menstrual cycle. A secondary objective of this study was to identify whether performance across menstrual cycle would differ between eumenorrheic females (OCP non-users) and OCP users.

2. Methods

This study used a single-blinded prospective counterbalanced repeated measures design. Thirty-six healthy college females with normal menstrual cycles (24 OCP users, 12 eumenorrheic females) were recruited to participate in this study (age = 21.4 ± 1.7 years; height = 166.23 ± 7.22 cm; mass = 63.02 ± 8.41 kg). A regular menstrual cycle was defined as lasting 25–35 days consistently for a period of 12 consecutive months leading up to and including the time of enrollment. Females with a history of concussion, balance or vestibular disorders, or lower extremity injury during the 3 months prior to enrollment, were excluded from participation in this study. Knowingly pregnant females, those diagnosed with premenstrual syndrome or experiencing amenorrhea (absence of menstruation) or oliomenorrhea (irregular menstrual cycles) at any time during the past 12 months and females using OCPs for less than 3 months prior to the study, were excluded from participating.

Qualifying participants were classified into one of two groups: OCP user or eumenorrheic female. Eumenorrheic females were asked to track their menstrual cycle on a daily basis, determine the onset date and duration of menstrual flow, and provide the anticipated dates of their follicular (early) and luteal (late) phases. By convention, the first day

of menstruation (flow) defined the start of a new menstrual cycle. At that time, their testing order was counterbalanced with one session taking place during the early phase (i.e. 3–5 days after the cessation of menstrual flow) and the other session taking place during the late phase (i.e. 4–6 days prior to the onset of menstrual flow). The start and end of menstrual flow were confirmed; if a participant did not accurately anticipate the start of her menstrual cycle, they were eliminated from the study. This occurred on six occasions, decreasing our eumenorrheic sample to a total of 12 females. Participants read and completed human ethics approval forms approved by the university's institutional review board.

The Immediate Postconcussion Assessment and Cognitive Test (ImPACT) is a computer-administered neuropsychological test battery consisting of seven individual test modules that measure aspects of cognitive functioning including attention, memory, reaction time and information processing speed. The verbal and visual memory composite indices, reaction time, visual motor speed and symptom scores, were retained for analysis. There are five alternate forms of the ImPACT, with differing word and design memory stimuli, alternating for each of these five forms. The stimuli are infinitely randomised (including the stimuli for each alternate form) each time the test is given, further circumventing the typical practice effects associated with paper-and-pencil testing. Research has shown there to be no practice effects for three of four composite scores, with the visual motor (information processing) speed composite score having a minimal 3-point practice effect from time 1 to time 2.¹³ The ImPACT is a reliable¹³ and valid¹⁴ tool used in the assessment of concussion, and has previously demonstrated good sensitivity and specificity.¹⁵

Included in the ImPACT is a Postconcussion Symptom Scale (PCSS) designed to evaluate both the presence and severity of 22 symptoms commonly associated with concussion. The PCSS uses a Likert scale for each symptom, ranging from 0 (asymptomatic) to 1 (mildly symptomatic) to 6 (severely symptomatic). Participants completed the PCSS based on how they were feeling at the testing time. A total severity score was computed and reported within the ImPACT software by summing all the individual severity scores across the 22 symptoms. We manually reviewed each test report in order to determine the number of separate symptoms endorsed, regardless of their respective severity. Both total symptom severity and total number of symptoms endorsed were retained as outcome measures for the purposes of our data analyses.

The Sensory Organization Test (SOT; NeuroCom International Inc., Clackamas, OR) was used to assess participants' balance performance during both phases of their menstrual cycle. The SOT is able to assess balance performance by disrupting input from the visual, vestibular and somatosensory systems. The participants stood with feet shoulder width apart on the force platform with arms comfortably at both sides. Participants were then asked to complete three 20-s trials of six different sensory conditions in random order. The SOT

has been previously described in detail.¹⁶ The outcome measures of interest were the overall composite scores, and ratio scores for somatosensory, vestibular and visual components of balance.

The primary investigator administered testing while being blinded to the participants' current menstrual cycle phase and group assignment. All participants completed computerised neurocognitive testing using the ImPACT sports-concussion management software. This was performed in an enclosed area in order to limit outside influences or distractions that may influence the participants' performance. Once the ImPACT testing was completed, results for verbal and visual memory composite indices, reaction time, visual motor processing speed, total symptom severity and total number of symptoms endorsed, were recorded.

The SOT was then administered to each female. Participants performed six different balance tasks, all of which were completed using double-leg stances. These tasks were performed in random order. Each trial was performed for 20 s, with a 15-s rest period between trials. The trials were repeated three times. The SOT automatically computes ratio scores for visual, somatosensory and vestibular performance, as well as an overall composite equilibrium score.

Procedures delineated in the first testing session section were repeated. A different word list for the ImPACT was used in the second test session. All testing was initially designed to occur within one menstrual cycle. In five cases, testing was accomplished over two menstrual cycles to capture the correct phase.

Separate 2×2 ANOVAs with menstrual cycle phase (early and late) and use of OCP (OCP user or eumenorrheic female) as the independent variables were performed with the following outcome measures: ImPACT testing (verbal memory, visual memory, reaction time, and visual motor processing speed), PCSS assessment (total symptom severity and total number of symptoms endorsed), and the Neuro-Com SOT (composite equilibrium score). A group \times phase MANOVA was performed on the following dependent measures: somatosensory, visual, and vestibular ratio scores. An a priori level of significance was set at $P < 0.05$.

3. Results

There were no differences in age ($P = 0.947$), height ($P = 0.597$), and body mass ($P = 0.718$) between OCP users and eumenorrheic females. Descriptive neuropsychological, symptomatology and postural stability test data are provided in Table 1. No significant interaction effects between phase of menstrual cycle and use of OCP were observed for the following neuropsychological test outcome measures: verbal memory ($P = 0.706$), visual memory ($P = 0.747$), visual motor processing speed ($P = 0.369$) and reaction time ($P = 0.421$). Main effects for menstrual cycle phase ($P > 0.05$) and OCP use were also not observed ($P > 0.05$) for any of the outcome measures. Eumenorrheic females experienced a

significantly higher total symptom severity score ($P = 0.001$) and number of symptoms endorsed ($P < 0.001$) than OCP users. However, no significant interaction effects between menstrual cycle phase and use of OCP were observed for our symptom outcome measures: total symptom severity score ($P = 0.511$) and number of symptoms endorsed ($P = 0.944$). No effect of menstrual cycle phase on total symptom severity score ($P = 0.289$) or number of symptoms endorsed ($P = 0.368$) was observed. No significant interaction effects between phase of menstrual cycle and use of OCP were observed for the following postural stability outcome measures: somatosensory ratio score ($P = 0.070$), visual ratio score ($P = 0.899$), vestibular ratio score ($P = 0.685$), and composite equilibrium score ($P = 0.546$). Main effects for menstrual cycle phase ($P > 0.05$) and OCP use were also not observed ($P > 0.05$) for any of the outcome measures.

4. Discussion

To our knowledge, this study is the first to investigate changes in common clinical measures of concussion between the early and late stages of the menstrual cycle in healthy college-aged females; and to identify whether performance across menstrual cycle phase differed between eumenorrheic females and OCP users. The most important finding was that clinical measures of concussion remained consistent throughout the menstrual cycle, supporting the idea post-injury testing could be compared to baseline scoring obtained at any phase of the menstrual cycle. Our data also suggest eumenorrheic females report more symptoms and total symptom severity compared to OCP users, regardless of menstrual cycle phase.

Clinical measures of verbal memory, visual memory, visual motor processing speed, and reaction time were stable across menstrual cycle phase in healthy female collegiate students. An impairment in verbal fluency and improved reaction time in the luteal phase compared to the follicular phase were reported in females not suffering from premenstrual syndrome (PMS).⁸ The opposite effect was observed in another study reporting increased verbal fluency measures in the late luteal phase.¹⁷ Our finding of no significant phase or group differences in reaction time between OCP users and OCP non-users in the ovulatory (days 10–16) and post-ovulatory (days 17–25) phases (corresponding to our early and late phases) is supported.¹⁸

Our data suggests the number and severity of symptoms remain unchanged across menstrual cycle phase in a young healthy female college sample, but seem to be more pronounced in eumenorrheic females. This disagrees with previous work reporting females endorsed more PMS symptoms during the follicular phase compared to the late luteal phase of menstruation.¹⁹ The discrepancy may be that the latter report studied premenstrual symptoms while we included symptoms more commonly experienced by concussed ath-

Table 1
Means (S.D.) for neuropsychological testing, symptomatology assessment, and postural stability testing outcome measures

Outcome measures	OCP users (n = 24)		Eumenorrhic females (n = 12)		Interaction effect, P value	Group effect, P value	Phase effect, P value
	Early phase	Late phase	Early phase	Late phase			
Neuropsychological testing							
Verbal memory	92.08 (6.29)	93.08 (5.60)	92.17 (6.37)	93.92 (5.33)	0.706	0.061	0.173
Visual memory	80.46 (10.64)	79.21 (10.82)	81.58 (12.52)	81.42 (9.89)	0.747	0.635	0.673
Visual motor processing speed	45.56 (6.87)	46.68 (5.50)	44.68 (6.09)	44.11 (6.04)	0.369	0.390	0.770
Reaction time	0.526 (0.056)	0.520 (0.065)	0.533 (0.042)	0.540 (0.049)	0.421	0.461	0.962
Symptomatology							
Total symptom severity score	2.83 (3.32)	3.21 (3.49)	8.00 (6.11)	9.58 (9.24)	0.511	0.001 ^a	0.289
Total symptoms endorsed	1.96 (2.03)	2.54 (2.43)	5.08 (3.20)	5.58 (3.92)	0.944	<0.001 ^a	0.368
Postural stability testing^b							
Somatosensory ratio score ^c	97.58 (2.17)	96.96 (2.14)	96.33 (5.21)	98.33 (1.92)	0.070	0.930	0.338
Visual ratio score ^c	93.79 (7.49)	92.83 (9.23)	91.58 (11.45)	90.00 (12.90)	0.899	0.307	0.605
Vestibular ratio score ^c	79.96 (8.74)	78.92 (11.16)	78.50 (9.68)	79.42 (7.68)	0.685	0.843	0.979
Composite equilibrium score	85.49 (6.41)	83.85 (6.73)	83.89 (7.49)	83.37 (8.46)	0.546	0.657	0.245

^a Eumenorrhic females higher than OCP users.

^b Somatosensory, visual, and vestibular ratio scores presented in percentages.

^c MANOVA results for this analysis ($F_{3,66} = 1.391$, $P = 0.253$); individual step-down ANOVAs for these variables are presented in this table.

letes. Lending support to our findings, eumenorrhic females exhibit an increase in mood-related symptoms and depression scores compared to OCP users.²⁰ Although we observed a twofold to threefold increase in symptom severity, our mean severity score for eumenorrhic females (8.79) and OCP users (3.02) is in line with previously published pre-season baseline total symptom severity scores.²¹

Postural stability appears unaffected by both use of OCP and menstrual cycle phase, highlighting a number of important clinical implications. First, it demonstrates the NeuroCom SOT is a stable measure of balance performance in healthy collegiate females. Secondly, any deficits in post-injury postural stability test measures may likely be due to the suspected concussion rather than menstrual cycle phase. Published studies investigating postural stability in concussed athletes have shown deficits lasting as long as 3–5 days post-injury;^{16,22} our sample was comprised of healthy uninjured collegiate students and changes were not expected. Friden et al.⁵ demonstrated no postural sway differences in females not experiencing PMS across the luteal, follicular, and ovulation phases of the menstrual cycle. This study was limited by sample size, and its sample differed significantly from ours (PMS vs. non-PMS compared to eumenorrhic female and OCP user), rendering any direct comparisons difficult. Clinicians should be confident in using postural stability testing as part of their concussion assessment and management protocols.

While we were consistent in our approach to scheduling, we relied on the self-reported anticipatory start date of menstrual flow (which was later confirmed) and recognise that performing blood draws to measure hormone levels or measuring body temperature would have allowed us to more accurately identify whether our participants were in a particular phase of their menstrual cycle. Certified athletic trainers and physicians rely on their athletes' self-report of

this information, rendering our study clinically applicable. Our unbalanced design reflected the disproportionate number of female athletes at our institution using some form of OCP. Our study excluded females experiencing menstrual dysfunction or severe PMS; future research should study the effects of these conditions on clinical measures of concussion in exercising populations. We included females using monophasic or triphasic estrogen–progestin combination OCPs. While some speculation exists in the literature as to how alterations in hormone concentrations might have affected our outcome measures, our non-significant findings between OCP users and eumenorrhic females suggest different types of combination OCPs have little effect in this regard. Finally, our study could also have benefited from the inclusion of a male control group.

In summary, common clinical measures of concussion do not differ across the early and late phases of the menstrual cycle. While eumenorrhic females report more severe symptoms, differences on all measures of cognition and balance should not be expected. This study supports a single baseline measurement is clinically stable across menstrual cycle phase, and investing time to complete multiple baseline measurements is not required. At this time, we are unable to rule out balance, cognitive, and symptom differences between women with and without PMS. We encourage clinicians to understand the cyclic tendencies of their female athletes and patients, recognising women with PMS may behave very differently.

Practical implications

- Sports medicine professionals should adopt a multifaceted approach to diagnosing and managing sports-related concussion.

- When completing a thorough medical history with female athletes, clinicians should give attention to oral contraception use and documenting irregular menstrual cycles.

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References

- Langlois JA, Rutland-Brown W, Wald MM. The epidemiology and impact of traumatic brain injury: a brief overview. *J Head Trauma Rehabil* 2006;**21**(5):375–8.
- Lovell MR, Collins MW, Iverson GL, Field M, Maroon JC, Cantu R, et al. Recovery from mild concussion in high school athletes. *J Neurosurg* 2003;**98**(2):296–301.
- Covassin T, Swanik CB, Sachs M, Kendrick Z, Schatz P, Zillmer E, et al. Sex differences in baseline neuropsychological function and concussion symptoms of collegiate athletes. *Br J Sports Med* 2006;**40**(11):923–7.
- Mihalik JP, Stump JE, Lovell MR, Collins MW, Norwig J, Hagan T, et al. Sex differences in acute recovery following concussion in athletes. *Br J Sports Med* 2004;**38**(5):661.
- Friden C, Hirschberg AL, Saartok T, Backstrom T, Leanderson J, Renstrom P. The influence of premenstrual symptoms on postural balance and kinesthesia during the menstrual cycle. *Gynecol Endocrinol* 2003;**17**(6):433–9.
- Möller-Nielsen J, Hammar M. Women's soccer injuries in relation to the menstrual cycle and oral contraceptive use. *Med Sci Sports Exerc* 1989;**21**(2):126–9.
- Myklebust G, Maehlum S, Holm I, Bahr R. A prospective cohort study of anterior cruciate ligament injuries in elite Norwegian team handball. *Scand J Med Sci Sports* 1998;**8**(3):149–53.
- Symonds CS, Gallagher P, Thompson JM, Young AH. Effects of the menstrual cycle on mood, neurocognitive and neuroendocrine function in healthy premenopausal women. *Psychol Med* 2004;**34**(1):93–102.
- Morgan M, Rapkin AJ, D'Elia L, Reading A, Goldman L. Cognitive functioning in premenstrual syndrome. *Obstet Gynecol* 1996;**88**(6):961–6.
- Hampson E. Estrogen-related variations in human spatial and articulatory-motor skills. *Psychoneuroendocrinology* 1990;**15**(2):97–111.
- Hampson E. Variations in sex-related cognitive abilities across the menstrual cycle. *Brain Cogn* 1990;**14**(1):26–43.
- Gordon HW, Lee PA. No difference in cognitive performance between phases of the menstrual cycle. *Psychoneuroendocrinology* 1993;**18**(7):521–31.
- Iverson GL, Lovell MR, Collins MW. Interpreting change on ImPACT following sport concussion. *Clin Neuropsychol* 2003;**17**(4):460–7.
- Iverson GL, Lovell MR, Collins MW. Validity of ImPACT for measuring processing speed following sports-related concussion. *J Clin Exp Neuropsychol* 2005;**27**(6):683–9.
- Schatz P, Pardini JE, Lovell MR, Collins MW, Podell K. Sensitivity and specificity of the ImPACT Test Battery for concussion in athletes. *Arch Clin Neuropsychol* 2006;**21**(1):91–9.
- Guskiewicz KM, Ross SE, Marshall SW. Postural stability and neuropsychological deficits after concussion in collegiate athletes. *J Athl Train* 2001;**36**(3):263–73.
- Maki PM, Rich JB, Rosenbaum RS. Implicit memory varies across the menstrual cycle: estrogen effects in young women. *Neuropsychologia* 2002;**40**(5):518–29.
- Garrett KF, Elder ST. The menstrual cycle from a bio-behavioral approach: a comparison of oral contraceptive and non-contraceptive users. *Int J Psychophysiol* 1984;**1**(2):209–14.
- Ross C, Coleman G, Stojanovska C. Prospectively reported symptom change across the menstrual cycle in users and non-users of oral contraceptives. *J Psychosom Obstet Gynaecol* 2003;**24**(1):15–29.
- Abraham S, Luscombe G, Soo I. Oral contraception and cyclic changes in premenstrual and menstrual experiences. *J Psychosom Obstet Gynaecol* 2003;**24**(3):185–93.
- Mihalik JP, Stump JE, Collins MW, Lovell MR, Field M, Maroon JC. Posttraumatic migraine characteristics in athletes following sports-related concussion. *J Neurosurg* 2005;**102**(5):850–5.
- Guskiewicz KM. Assessment of postural stability following sport-related concussion. *Curr Sports Med Rep* 2003;**2**(1):24–30.