HHS Public Access

Author manuscript

J Head Trauma Rehabil. Author manuscript; available in PMC 2017 January 15.

Published in final edited form as:

J Head Trauma Rehabil. 2014 ; 29(5): E1–E8. doi:10.1097/HTR.0000000000000006.

Menstrual Phase as Predictor of Outcome After Mild Traumatic Brain Injury in Women

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Abstract

Objective—To determine whether menstrual cycle phase in women at the time of mild traumatic brain injury (mTBI) predicts 1-month outcomes.

Setting—Six emergency departments; 5 in Upstate New York, and 1 in Pennsylvania.

Participants—One hundred forty-four female participants (age, 16–60) who presented to participating emergency departments within 4 hours of mTBI.

Design—Nested cohort study with neurologic and quality-of-life outcome assessment, 1 month after enrollment. Female subjects aged 16 to 60 enrolled in the parent cohort study, with 1-month neurological determination data available, were classified into menstrual cycle groups by serum progesterone concentration and self-reported contraceptive use.

Main Measures—Rivermead Post Concussion Questionnaire and EuroQoL/EQ5D.

Results—Women injured during the luteal phase of their menstrual cycle, when progesterone concentration is high, had significantly lower EuroQoL General Health Ratings and Index Scores than women injured during the follicular phase of their cycle or women taking oral contraceptives. Multivariate analysis confirmed a significant independent effect of menstrual cycle phase on EuroQoL Index Score and the Rivermead Post Concussion Questionnaire Somatic Subscore.

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The remaining authors declare no conflicts of interest.

Conclusion—Menstrual cycle phase and progesterone concentration at the time of mTBI affect 1-month quality-of-life and neurologic outcomes. This association has important implications for treatment and prognosis after mTBI.

Keywords

brain concussion; brain injuries; follicular phase; luteal phase; menstrual cycle; postconcussion syndrome; progesterone; quality of life

Traumatic brain injury (TBI) can have long-lasting effects on patients' cognition and functioning. The impact of TBI is not limited to the severely injured; even patients with mild traumatic brain injury (mTBI) report long-term sequelae, such as memory and concentration problems.[1] Although recent popular press has primarily focused on mTBI in male professional athletes and veterans, studies suggest that women have a higher incidence of mTBI than men playing sports with similar rules, such as ice hockey, soccer, or basketball.[2,3] Although it is unclear whether this apparent increased risk represents reporting bias or a physiologic difference, additional research suggests that women have worse outcomes than men following mTBI. Trying to understand what causes these gender differences in outcomes could help to inform prognosis and treatment after injury.

Gender-based differences in TBI outcome have long been recognized but incompletely understood. Experimentally-induced TBI in rodent models has revealed that females experience less cerebral edema, better cerebral blood flow, and overall survival than males.[4,5] However, studies in humans have found the opposite. After mTBI, women have higher postconcussive symptom scores,[6,7] greater cognitive decline,[8] and poorer reaction time compared to baseline[9] then do men. A meta-analysis of 8 studies of gender differences in outcomes after TBI of all severities showed that women experienced worse outcomes in 17 out of 20 variables measured.[10] These variables included death, length of hospitalization, headache, depression, and return to work. Other studies have found better post-TBI outcomes for women than men, but among premenarche or postmenopausal women.[11,12]

These findings suggest sex hormones, such as estrogen and progesterone, mediate outcome after TBI. Because women of childbearing age have the worst outcomes following TBI and possess the highest concentration of these hormones, it would not be unreasonable to speculate that an increase in estrogen and progesterone would be associated with poor outcome following TBI. However, 2 phase II clinical trials using progesterone to treat TBI have shown improved outcome in those receiving progesterone, although results were not broken down by gender.[13,14] If progesterone is indeed neuroprotective, it becomes more difficult to explain the poorer outcomes observed among women during a life phase of high progesterone and estrogen levels. Studies on changes in sex hormone levels following TBI may hold an explanation. A study by Ripley et al revealed that women frequently miss menstrual periods or experience total amenorrhea after TBI, suggesting postinjury deficits in sex hormones.[15] Other studies have more definitively shown that the hypothalamic-pituitary-gonadal axis becomes suppressed after TBI, ultimately decreasing luteinizing hormone, follicle-stimulating hormone, testosterone, progesterone, and estrogen concentrations.[16] Therefore, although sex hormones and progesterone in particular, may be protective, their

sudden withdrawal after injury may be the key factor contributing to worse outcomes in women. Because males have low preinjury levels of these hormones, they are ostensibly less affected by TBI-related suppression of the hypothalamic-pituitary-gonadal axis. This withdrawal hypothesis could therefore simultaneously explain why women generally have worse outcomes than men, and why administration of exogenous progesterone may be protective.

One way of considering this hypothesis is to relate post-TBI outcomes to the menstrual cycle phase during which the injury occurs. Progesterone concentration varies predictably during the menstrual cycle, with the highest concentration during the luteal phase (LP), and the lowest concentration during the follicular phase (FP) (see Figure 1). In addition, many women now take hormonal forms of birth control, which provide constant high levels of synthetic progestins.

We hypothesized that women who experience mTBI during the LP of their menstrual cycles, when progesterone is high, will have worse outcomes than women injured during the FP of their menstrual cycles, when progesterone is low. Furthermore, we expected women taking birth control that contained synthetic progestins to have similar outcomes to those injured in the FP of their menstrual cycle. To test this hypothesis, we sought to determine the relationship of menstrual cycle phase, confirmed by progesterone concentration, at the time of mTBI to neurologic and quality-of-life (QoL) outcomes 1-month postinjury in women.

METHODS

Design and setting

We conducted a nested cohort study of women with mTBI presenting to emergency departments within 4 hours of injury. The parent study was a prospective, multicenter, cohort study exploring the accuracy of a serum marker, S100B, for identifying traumatic abnormalities on head computed tomography (CT) scan after mTBI. Participants were enrolled in the parent study at 5 hospitals in Upstate New York and 1 hospital in Pennsylvania between 2008 and 2010. Subjects were eligible for inclusion in the parent study if they were 1 year of age and older, had mTBI as defined by the Centers for Disease Control and Prevention's National Center for Injury Prevention and Control (a blow to the head or rapid acceleration/deceleration resulting in at least 1 of the following: a loss of consciousness ≤30 minutes, posttraumatic amnesia ≤24 hours, neuropsychological abnormality [any transient period of confusion, disorientation, or impaired consciousness; in children ≤2 years old: irritability, lethargy, or vomiting postinjury], or neurological abnormality [seizure acutely following injury, hemiplegia, or diplopia]).[17] Additional inclusion criteria included arrival to the emergency department within 4 hours of injury, and performance of head CT scanning as part of their clinical care.

Participating subjects were interviewed in the emergency department for information regarding their injury (mechanism; time of injury; initial symptoms such as loss of consciousness, amnesia, and headache), demographics (age, gender, race, ethnicity, income level, weight) and medical history (including prior head injury, medications, and last menstrual period). The emergency provider was also interviewed, and the emergency chart

was reviewed to determine associated injuries and Glasgow Coma Scale score. Subjects had blood drawn within 6 hours of injury. The blood was centrifuged, and the resulting serum was stored at −70°C within 1 hour of collection. In addition, head CT results were obtained, and, in subjects older than 16 years, 1-month outcome was assessed by phone using the Rivermead Post Concussion Questionnaire (RPCQ) and EuroQol/EQ5D (described in the text hereafter).

Participants

Subjects were selected from the parent study into this nested cohort if they were female, between the ages of 16 and 60, and had neurologic outcome determination 1 month after injury. Because serum progesterone was used to confirm menstrual cycle phase, only subjects who had provided serum were included. In addition, subjects who were postmenopausal were excluded. Post-menopausal status was confirmed by follicle-stimulating hormone concentration more than 15 mIU/mL in all subjects who were older than 45 years, and in subjects who reported a hysterectomy, or reported being post-menopausal.

Menstrual cycle phase at the time of injury

Serum progesterone level was used to determine the menstrual cycle phase at the time of injury. Menstrual cycle phase was defined in the following manner: FP: serum progesterone concentration 2 ng/mL or less; and LP: serum progesterone concentration more than 2 ng/mL. A cutoff of 2 ng/mL was chosen as progesterone usually rises to over 1.5 ng/mL at ovulation and is higher throughout the LP.[18] Progesterone concentration was not measured in those reporting synthetic progestin use, such as any oral contraceptive, Mirena IUD (Bayer; Wayne, New Jersey), Depo Provera (Pfizer, New York), or levonorgestral implants. On the basis of the results, subjects were divided into 3 groups: synthetic progestin (SP) group, FP group, and LP group.

One-month neurologic and QoL outcome determination

The primary outcome of interest was postconcussion symptoms 1 month after injury. These were determined by the RPCQ. The RPCQ is a 16-question validated self-report measure that assesses postconcussive symptoms on a 4-point Likert scale ranging from absent (0) to severe (4).[19] Thus, the total scores range from 0 to 64. RPCQ scores were also categorized into 3 individual domains, as described by previous factor analysis: somatic, cognitive, and emotional.[20]

Secondary outcomes included QoL at 1 month, as determined by the EuroQol/EQ5D. This is a standardized instrument used as a measure of health outcome. Applicable to a wide range of health conditions and treatments, it provides a simple descriptive profile and a single index value for health status. The total score comprises items representing 5 domains of health: mobility, self-care, usual activity, pain, and emotional health. Each of the 5 domains is categorized into 3 severity levels: “no problems,” “moderate problems,” and “extreme problems.” Values for health states are based on time trade-off responses taken from a sample of the US population, which form an EuroQoL Index Score.[21] Euro-QoL/EQ5D is designed for self-completion by respondents, but can also be administered in a face-to-face

interview, a telephone interview, or through a proxy. In this study, the measure was administered by telephone. In addition to questions in the 5 domains, patients are asked to rate their general health on a scale from 0 to 100, with 100 being best health imaginable and 0 being worst. The EuroQoL Index Score and the General Health Rating were used as 2 separate outcomes in the current analysis.

Covariates

Several factors other than menstrual cycle phase at the time of injury can influence outcome after mTBI. These include age, race, history of concussions, mechanism of injury dichotomized as “severe” (motor vehicle accident with ejection or pedestrian struck by vehicle) or “not severe” (all other mechanisms), the presence of traumatic abnormality on CT scan (defined as subdural, subarachnoid, or epidural hemorrhage; contusion; edema; or skull fracture), and the presence of any other extra-cranial injuries. These were all considered as possible covariates in determining the independent effect of estrous cycle phase on post-mTBI outcome. Race, concussion history, and presence of other injuries were all associated with at least 1 outcome at a level where $P < .2$ and were included in all models. Although the menstrual cycle phase groups were different with regard to age and CT scan result, these variables were not associated with any of the outcomes and were therefore not included in the multivariable models.

Statistical analyses

None of the variables were normally distributed, so difference in mean RPCQ, cognitive, somatic, and emotional RPCQ subscores, EuroQoL Index Score, and EuroQoL General Health Ratings were compared among the SP, FP, and LP groups using the Kruskal-Wallis test. If the Kruskal-Wallis tests were significant, the Dunn post-hoc test was used to compare values between each of the group pairs.

For outcomes associated with menstrual cycle phase in the 1-way analysis of variances or Kruskal-Wallis test at $P < .2$, a multivariable regressions was performed to adjust for potential confounders. Because of the skewed nature of the scores on the scales, scores were grouped into tertiles, and ordinal logistic regression was used to control for covariates that were associated with the any of the outcomes at $P < .2$. The FP group was used as the reference group for all analyses because of its larger sample size. For all models, the proportional odds assumption was checked using the likelihood ratio test.

All significance tests were 2-sided, and $P \leq .05$ values were considered significant. Analyses were performed using Statistical Analysis Software (SAS), version 9.2 (SAS Institute Inc., Cary, NC), and GraphPad Prism, version 5 (GraphPad Software Inc., La Jolla, CA).

RESULTS

Of the 787 patients with mTBI in the parent study, 189 (24%) were females between the age of 16 and 60 with complete 1-month neurologic outcome data. Sixty-one patients were excluded because of lack of 1-month outcome data. Compared with included patients, there was no significant difference in the proportion of these excluded patients in the LP (19.7% vs 30.6%, $P = .12$) or in the FP (29.5% vs 36.1%, $P = .42$), based on self-report of last

menstrual period date. Forty-five patients were excluded as postmenopausal by follicle-stimulating hormone analysis (see Figure 2). Of the resulting 144, 35 fell into the SP group based on self-reported synthetic progestin use. On the basis of progesterone concentration, 37 fell into the LP group and 72 in the FP group. Group characteristics are shown in Table 1. The subjects in the SP group were younger than those in the other group, were less likely to have a positive CT scan, and were more likely to be non-Hispanic white than those in the other groups.

Neurologic outcomes varied in the 3 estrous cycle groups. The EuroQoL Index Score was significantly different among groups ($P = .0106$), with the SP group having the highest score (0.8663) and the LP group having the lowest score (0.7403). The Dunn test indicated that this difference between the SP and LP groups was significant ($P < .05$). The differences between the other pairs were not significant. The difference in EuroQoL General Health Rating was also significant ($P = .0357$) with the SP group again having the highest score (77.14) and the LP group again having the lowest score (65.14). Again, the Dunn test indicated that the difference between the SP and LP groups was significant ($P < .05$), while the difference between the other pairs were not significant. In terms of the RPCQ results, the LP group was the most symptomatic of the 3 groups, but across all measures, none of these differences were statistically significant.

The independent effect of estrous cycle phase on outcome is shown in Table 2. Phase of menstrual cycle was significantly associated with EuroQoL Score and the somatic component of the RPCQ. For all outcomes, subjects in the LP had approximately twice the odds of scoring in a worse tertile on the outcome scales than subjects in the FP. There was no clear difference in outcome between the subjects on synthetic progestin and subjects in the FP.

DISCUSSION

Although several studies have shown differences in outcome after mTBI between men and women, few studies have explored why such differences occur. One theory, here, referred to as the “withdrawal hypothesis,” postulates that TBI occurring in the setting of high progesterone (which is neuroprotective) results in a sudden progesterone decrease and worse outcomes compared with TBI occurring in the setting of low progesterone. Women therefore experience worse outcomes than men because men have a consistently low concentration of progesterone. The results of our study support this hypothesis, as women in the LP of the menstrual cycle, in which progesterone is highest, had worse postconcussion symptoms and QoL 1 month after injury than women in the FP of menstrual cycle, in which progesterone is initially low and can therefore not decrease significantly. Similarly, women who were taking synthetic progestin as birth control when they experienced mTBI, and therefore had high levels of progestin during and after the injury, had QoL scores 1 month after the injury that were no different than those of women who were in the FP of their menstrual cycle.

Our results are novel but must be considered preliminary. Few prior studies have been done to explore the relationship between estrous cycle phase and post-TBI outcome. Estrous cycle phase was not shown to predict outcomes in rat cortical impact models,[22] and a decrease in

progesterone concentration following severe TBI did not predict mortality.[23] We could find no prior reports investigating whether sex hormones, as measured by progesterone concentration or menstrual cycle phase, are associated with outcome after mTBI in humans. In addition, we were unable to find any reports exploring whether synthetic progestins such as the progestin-only minipill, which would confer a constant high level of progestin after injury, have any protective effect after mTBI.

If our withdrawal hypothesis is confirmed by others, it has important implications for both treatment and prognosis. A serum screening test or question about date of last menstrual period might also offer significant prognostic information, indicating who is at risk for poor long-term outcomes and identifying patients who may be candidates for more aggressive monitoring or interventions. Women taking synthetic progestins at the time of the injury might be expected to have relatively good outcomes after injury, as long as they continue to take their birth control as before, because this would prevent any drop in progesterone. Women in the FP of their menstrual cycle at the time of the injury should also have relatively good outcomes, because their progesterone concentration would be low at the time of the injury and they would therefore experience little drop in progesterone. Women in the LP at the time of the injury, when progesterone concentration is high and variable, would be expected to experience the worst outcomes, because their progesterone concentration may drop after injury. Women in the LP of their menstrual cycle at the time of injury might then represent the best target for treatment with progesterone after TBI. If the withdrawal hypothesis is accurate, such a relatively simple intervention could lead to significant improvement in outcomes.

This study has many strengths, including confirming menstrual phase with hormone measurements taken from the time of injury, accurate case ascertainment, and complete follow-up. However, there are some limitations to this study, as well. The subjects were split very unevenly between the groups, with the FP group having about twice as many subjects as either the LP or SP group, instead of the approximately equal numbers of subjects in the FP and LP groups that had been expected. The increased size of the FP group might reflect an underreporting of synthetic progestin use. Women using synthetic progestins should have low levels of assayed progesterone, which would place them in the FP group, because the synthetic progestin suppresses the hypothalamic-pituitary-gonadal axis. If under-reporting explains the different group sizes, it still would not explain the worse outcomes for the LP group, but it does raise the possibility that women were inaccurate in reporting their use of birth control. The resultant small sample sizes in the LP and SP group also may have made it more difficult to determine statistical significance. Finally, women in the SP group tended to be younger and have slightly milder injury than women in the other groups. However, the improved outcomes for women in the SP group are not the result of age or of injury severity because these were not associated with the outcomes.

The differences seen in this study may have also been a result of symptom changes throughout the menstrual cycle, independent of any mTBI. Previous studies have indicated that women may be more susceptible to injury during the premenstrual phase of the menstrual cycle, which corresponds to the LP, than during the postmenstrual phases.[24] This difference in propensity to injury might be partially explained by physiological changes,

such as a proposed increase in anterior cruciate ligament laxity during the LP leading to increased likelihood of ligament injury,[25] or it could be explained by an increase in somatic symptoms. If the latter explanation is correct, then patients in certain phases of their menstrual cycle may report more symptoms than patients in other phases.[26] In this study, women in the LP at injury were likely to again be in the LP 30 days later at follow-up, so the difference in outcomes may have been a result of predictable differences in self-reported symptoms throughout the menstrual cycle, regardless of overall recovery. However, Mihalik et al[27] specifically explored whether women vary throughout their menstrual cycle on measures of neurocognition, balance, and postconcussive symptoms. They found that there was no variation in these more concussion-specific outcomes throughout the menstrual cycle, although women taking oral contraceptives tended to report fewer symptoms overall than those not taking oral contraceptives. The current findings in the SP group may therefore not represent an intervention specific to head injury, but may rather reflect reporting differences.

This study only provides preliminary support for the withdrawal hypothesis, and more research needs to be done to strengthen these findings. Replicating these results in a larger cohort and among patients with severe TBI is a useful first step. Measuring serum progesterone longitudinally after TBI in women might also provide more definitive proof of concept by tracking changes in progesterone to see how it correlates with outcome. Such a study would also clarify the time course of any potential withdrawal, thereby optimizing the timing of treatment.

In summary, phase of menstrual cycle as measured by progesterone concentration seems to be related to QoL and neurologic outcomes after mTBI. Women in the LP at the time of injury, when progesterone is highest, have worse outcomes than women in the FP, when progesterone is low, and women taking synthetic progestins. These results seem to support the hypothesis that the acute withdrawal of progesterone after mTBI may contribute to the gender differences seen after injury.

Now that gender differences in outcomes after TBI have been repeatedly recognized, research should continue to explore why those differences occur. Such knowledge has the potential to elucidate causes of disability after injury, as well as improve patient care and outcomes.

Acknowledgments

Jeffrey J. Bazarian has received consulting fees from Banyan Biomarkers and Roche Diagnostics. Jeffrey J. Bazarian was supported by funds from the New York State Department of Health, the Academic Health Center Consortium, and the Emergency Research Network of the Empire State (ERNIES). ERNIES is supported by the Pilot Research Collaborative Program of the Foundation for Healthy Living, the University of Rochester's Clinical and Translational Science Award, the Upstate New York Translational Research Network (UNYTRN) and the Upstate New York Consortium for Healthcare Research and Quality (UNYCHRQ).

The authors thank Liana Dypka, Nancy Robak, MPH, RN, Donna Tyburczy, BSN, RN, Kamie Hoey, RN, and Coleen Vesely, RN, for their assistance and coordination in enrollment activities, and Akshata Nayak, Ming Ji, and Emily Tuttle, for processing serum samples.

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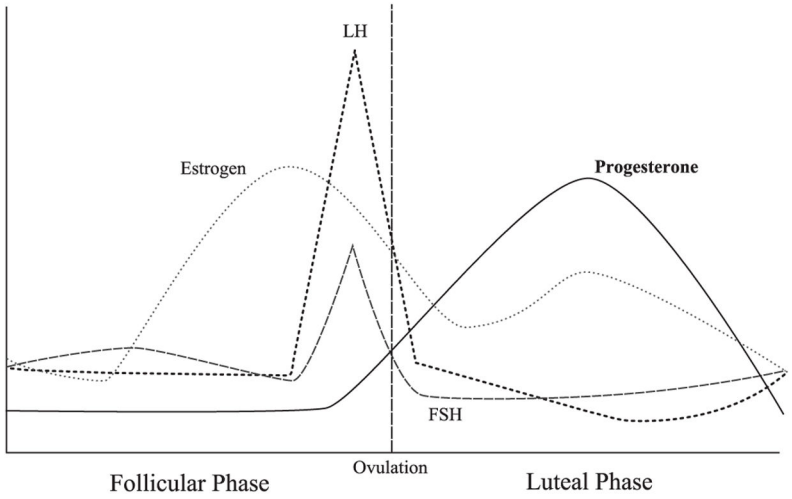

Figure 1.

Progesterone changes across menstrual cycle. Progesterone levels are very low during the follicular phase, but begin to rise just prior to ovulation. Levels peak and then fall during the luteal phase.

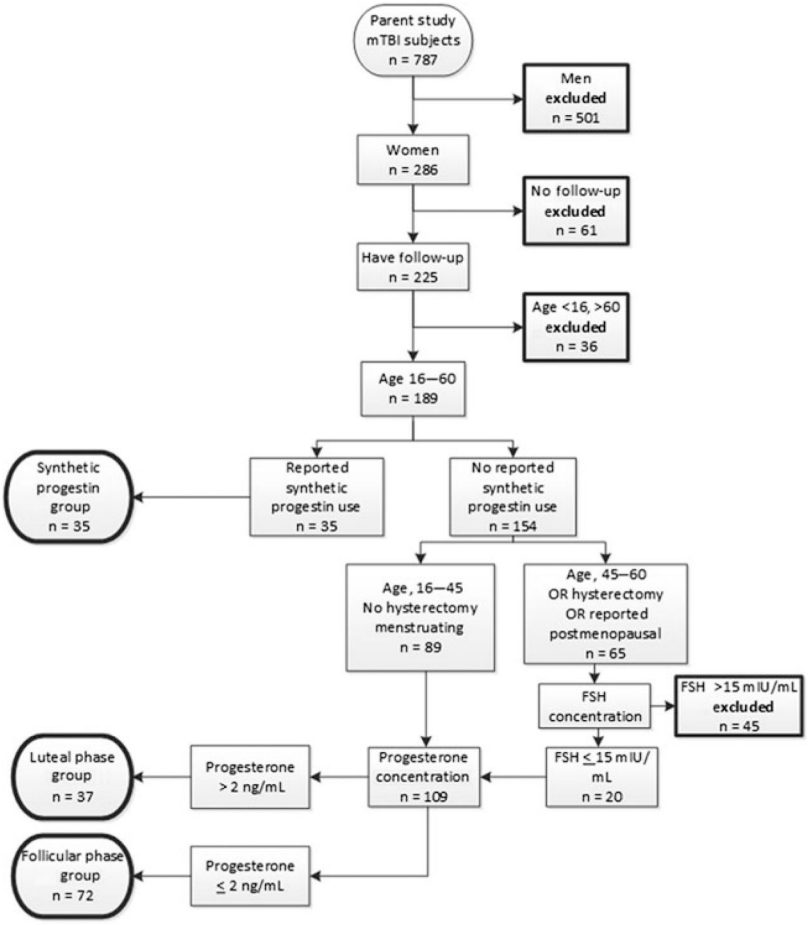

Figure 2.

Flowchart of patients included in study. Of the 787 mTBI patients in the parent study, 189 were females between the ages of 16 and 60, and 45 were excluded as postmenopausal by FSH analysis. Of the remaining 144 patients, 35 reported synthetic progestin use. On the basis of measured serum progesterone concentration, 37 subjects fell into the luteal phase group and 72 in the follicular phase group. FSH, follicle-stimulating hormone; mTBI, mild traumatic brain injury.

TABLE 1

Group characteristics

	LP ***n*** **= 37**	**FP** ***n*** **= 72**	**SP** ***n*** **= 35**
Age, mean (SD)	30.6 (10.17)	32.6 (11.11)	26.5 (9.28)
Race: non-Hispanic white, *n* (%)	24 (64.9)	42 (58.3)	33 (94.3)
GCS, mean (SD)	14.9 (0.35)	14.9 (0.40)	15 (0.0)
Previous concussion, *n* (%)	8 (21.6)	21 (29.2)	10 (28.6)
Other injuries, *n* (%)	13 (35.1)	24 (33.3)	12 (34.3)
Injury on CT scan, *n* (%)	1 (2.7)	2 (2.8)	0 (0.0)

Abbreviations: LP, luteal phase; FP, follicular phase; SP, synthetic progestin, SD, standard deviation; GCS, Glasgow Coma Scale; CT, computed tomography.

TABLE 2

Results of multivariable ordinal logistic regression; relative odds for scoring in a worse tertile on measures of postconcussive recovery

	RPCQ		RPCQ Somatic Subscore		EruoQoL Index Score		EuroQoL General Health Rating	
Parameter	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***
Menstrual cycle phase		0.15		0.05		0.04		0.13
Follicular phase (reference)	1		1		1		1	
Luteal phase	2.08 (0.98–4.41)		2.45 (1.15–5.24)		2.57 (1.18–5.58)		1.77 (0.83–3.79)	
Synthetic progestin	1.1 (0.50–2.43)		0.98 (0.44–2.18)		1.01 (0.43–2.36)		0.72 (0.32–1.59)	
Race		0.13		0.14		0.17	(0.59–2.93) (0.55–8.10)	0.48
White (reference)	1		1		1		1	
Black	2.17 (0.98–4.80)		2.2 (0.99–4.88)		1.88 (0.83–4.23)		1.32	
Other	1.95 (0.54–7.11)		1.71 (0.47–6.22)		0.51 (0.12–2.23)		2.11	
Concussion history (any vs none)	2.04 (1.01–4.14)	0.05	2.22 (1.09–4.53)	0.03	0.98 (0.47–2.04)	0.95	0.9 (0.45–1.80)	0.75
Other injuries (any vs none)	1.46 (0.76–2.81)	0.26	1.47 (0.76–2.85)	0.25	2.57 (1.30–5.10)	0.01	0.96 (0.50–1.86)	0.91

Abbreviations: CI, confidence interval; OR, odds ratio; RPCQ, Rivermead Post Concussion Questionnaire.