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# Exploring the relationship between contraceptive medication use and concussion recovery in female collegiate athletes: a LIMBIC MATARS consortium investigation

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## ABSTRACT

**Objective:** While recovery from concussion is variable, women are more likely to report symptoms, experience worse outcomes, and have longer recovery trajectories following concussion than men. Preliminary data suggest that hormonal fluctuations, specifically progesterone, may be associated with this variability. This study aimed to understand the effect of contraceptive medication on concussion recovery.

**Methods:** A retrospective chart review using consensus-based common data elements was conducted at 11 NCAA institutions as part of the LIMBIC MATARS consortium. Participants included female collegiate athletes diagnosed with a concussion who did ( $n = 117$ ) or did not report ( $n = 339$ ) contraceptive medication use. Number of days between diagnosis and symptom resolution were compared using Mann-Whitney U tests. Self-reported diagnosis of attention deficit hyperactivity disorder, concussion history, anxiety, and depression was compared using Chi-squared tests.

**Results:** The proportions of participants who did or did not take contraceptive medication were similar across covariates. Female athletes regardless of contraceptive medication use recovered similarly following a concussion.

**Conclusions:** Our findings suggest that contraceptive medication use did not significantly impact concussion recovery. Future prospective investigations should examine documentation practices and operationalize terminology for hormonal contraceptive medication to better understand their role on recovery from sport-related concussion in female collegiate athletes.

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Sports-related concussion; gender differences; sex differences; hormonal contraceptives; female athletes

## Introduction

The clinical presentation of concussion is highly variable and may include a range of symptoms, physical signs, transient interruptions in neurological function, balance deficits, and sleep disturbances (1,2). As with the clinical presentation of concussion, the trajectory of clinical recovery is also highly individualized. Symptom burden (i.e., quantity and severity), age, preexisting health conditions (e.g., anxiety and depression), history of prior concussion, and gender are documented modifiers of clinical recovery following concussion (3,4). Despite these modifiers of recovery, the majority of collegiate athletes have been observed to recover within 14-days of a concussion (5).

Gender and sex differences (dichotomized in research as men/male and women/female) in concussion have been identified in athletes through symptom reporting, recovery, and incidence (6–10). Specifically, women are more likely to report symptoms after a concussion and may experience longer recovery trajectories compared to men (6–10). Explanations for these differences include gender-based disparities such as

socialization to disclosure of suspected concussion, care seeking tendencies after injury, availability of resources, and pre-morbid symptom levels (11–15). Biologically based or sex-related differences that contribute to contrasts in concussion outcomes may include neck musculature girth, brain structure, and hormonal differences (16–20). However, further research is necessary to discern these mechanisms with limited research encompassing hormonal differences and the factors that may influence them, such as the use of contraceptive medication.

Significant fluctuations of hormones occur throughout a woman's menstrual cycle, and some hormones, including progesterone, may have neuroprotective effects on the brain (21). During the luteal phase (approximately Day 15 through Day 28 of the menstrual cycle), hormone concentration levels of estradiol and progesterone increase during the first half of the phase and decrease over the latter half of the phase. Preliminary research suggests that concussion frequency is higher during the end of the luteal phase as progesterone decreases (22). In addition, patient-reported quality of life is lower when a woman sustains a concussion during the luteal

phase when compared to the other phases of the menstrual cycle (23). In addition, adolescent self-reported symptom burden may be higher in the luteal phase several months after a concussion (24). It is hypothesized that these clinical findings may be due to declining levels of progesterone and estrogen (22). Alternatively, a sudden drop in progesterone levels due to injury may occur reducing potential neuroprotective effects. Increased symptom reporting and prolonged recovery trajectories may occur as a result of a rapid drop in progesterone, known as the progesterone withdrawal theory (23).

Hormonal contraceptives introduce synthetic versions of estrogen and/or progesterone. Prior research has identified neuroprotective associations of progesterone in human and animal models with moderate to severe traumatic brain injury (TBI) by reducing edema, cell death, and improving behavioral recovery (21,25,26). Two randomized clinical trials found positive outcomes for people with a moderate or severe TBI who received progesterone administration compared to a control group (27,28). Specifically, Wright and colleagues (27) observed an association of progesterone with decreased one-month post-injury disability ratings and mortality rate in patients with moderate TBIs. Xiao and colleagues (28) also observed better neurological outcomes and increased functional independence at three and six months post severe TBI as well as decreased mortality rate at six months for those who received a dose of progesterone after injury. Collectively, these results suggest that progesterone may play a positive role in clinical recovery from moderate to severe TBIs. However, the role of synthetic progesterone has on recovery from mild TBIs (i.e., concussion) is not yet fully delineated.

Hormonal contraceptives may provide one potential way to study the effects of progesterone after concussion. Based on previous research on moderate and severe TBI, exogenous progesterone may have a positive effect after brain injury (27,28). It is hypothesized that hormonal contraceptives may artificially elevate progesterone levels during phases of the menstrual cycle when it would naturally be lower or stabilize injury-related decreases in progesterone after concussion. To date, few studies have examined the effects of hormonal contraceptive use on recovery from sport related concussion, despite almost 65% of collegiate female athletes reporting the use of hormonal contraceptives (29). In the small body of literature that has examined hormonal contraceptive use and concussion recovery, women using hormonal contraceptives (reported as the use of oral contraceptive pill or NuvaRing®) endorsed fewer symptoms with lower symptom severity as compared to women not using hormonal contraceptives (30,31). However, the authors did not observe an association with recovery length. A separate study investigated the role of progesterone levels in women who were and were not using hormonal contraceptives, and identified an association between lower levels of perceived stress and higher levels of progesterone after a concussion (32). Notably, the study excluded women when the concussion occurred in the luteal phase, potentially providing further evidence for the progesterone withdrawal theory. However, these studies have included small sample sizes thereby limiting the generalizability of the results. More recently, a consortium study with a comparatively larger sample examined recovery metrics,

including self-report symptoms and length of recovery, between female athletes who did and did not report hormonal contraceptives (33). However, they did not identify differences on any recovery metrics.

The present study leveraged an even larger consortium sample to investigate the relationship between the timeline of symptom resolution from concussion in collegiate female athletes who did or did not report using contraceptives as a medication. While previous research has produced mixed results, we hypothesized that contraceptive medication use would be associated with a reduced number of days until symptom resolution among collegiate female athletes.

## Materials and methods

### Research design

This study was conducted through the LIMBIC (34) Military and Tactical Athlete Research Study (MATARS) consortium (35). Data were collected at 11 LIMBIC MATARS member sites using consensus-based common data elements. The 11 sites were similar in regard to their athletic department, consulting role, and able to access athletes' medical records from their respective university. All sites completed a confidentiality disclosure agreement, data use agreement and institutional review board approval. The common data elements were retrieved by paper and/or electronic files that were completed by athletic trainers, physicians, and other healthcare professionals who interacted with athletes prior to and following a diagnosed concussion between the 2015–16' and 2019–20' sport seasons. Provided the scope of this retrospective chart review, the questions used to collect the common data elements related to this study and all remaining studies were similar across study sites, however, each data point was dependent on the clinical protocol at each participating site. Based on retrospective chart review, we used a cross-sectional design to address our hypotheses.

The initial dataset consisted of 1,044 concussion cases. A common data element included operationally defined biological sex as the sex assigned at birth and was dichotomized as male and female. Information regarding individual gender identities were not available. Only concussion cases belonging to female athletes were included for analyses in the present study. Male athletes (56%) were excluded from the final dataset, resulting in 456 concussion cases of female athletes. Concussions were diagnosed in accordance with the International Concussion in Sport Consensus document or the National Athletic Trainers' Association Position Statement (1,36,37). Using a retrospective medical chart review, the status of contraceptive medication use and type, if available, was recorded with additional medications. Athletes who did not have contraceptive medication listed in their medical chart were recorded as 'not taking contraceptive medications'. Separating hormonal versus non-hormonal contraceptive use was unavailable for many athletes due to current data harmonization limitations. In addition, there was high variability in the types of contraceptive use that was reported. Athletes reported 22 different brand names and

over 50% of the sample did not report type and only indicated they were using ‘birth control’ medication.

Potential risk factors including race, attention deficit hyperactivity disorder (ADHD) diagnosis and/or learning disorder (LD), prior concussion history, and a history of anxiety or depression were recorded as part of the LIMBIC MATARS common data elements. Missing data included 159 for race, 72 athletes for ADHD/LD diagnoses, 23 athletes for concussion history, 128 athletes for depression, and 157 athletes for anxiety. Statistical analyses for each of these risk factors were run excluding only the missing data for each risk factor. Six athletes’ (one who reported and five who did not report contraceptive use) date of symptom resolution was reported prior to their date of diagnosis, likely due to late reporting. These six athletes were excluded from the analysis. Date of symptom resolution or date of diagnosis was missing for 79 (24 who reported and 55 who did not report contraceptive use) athletes and the statistical analysis for this outcome variable was run excluding this missing data.

### Statistical analysis

Mann-Whitney U and Chi-Squared ( $X^2$ ) analyses were used to compare groups based on demographic (age) and categorical variables (ADHD/LD, binarized concussion history, anxiety, and depression). Chi-Squared ( $X^2$ ) analyses were also done to identify missingness of demographic and pre-existing health conditions across both groups. The potential effect of contraceptive medication (independent variable, between factors with two levels: yes and no) was assessed across a primary dependent variable: time (in days) from date of diagnosis to symptom resolution. As our recovery data were non-normally distributed ( $p < 0.05$  for all Shapiro-Wilk tests) Mann-Whitney U tests were completed to compare female athletes by contraceptive medication use for the recovery time point. The Z values from the Mann-Whitney U tests were used to calculate nonparametric effect sizes ( $r = z/\sqrt{N}$ ) and were interpreted according to available guidelines (i.e.,  $r = 0.1$ , small;  $r = 0.3$ ,

medium;  $r = 0.5$ , large) (38,39). All analyses were performed using R Studio (40) with  $\alpha \leq 0.05$  *a priori*.

### Results

The initial LIMBIC MATARS dataset consisted of 456 concussion cases. A breakdown of athletes by sport can be found in Figure 1. Of the initial sample, 117 cases (25.5%; age:  $M = 19.6$ ,  $SD = 1.27$ ) reported contraceptives as a medication while 339 (74.3%; age:  $M = 19.4$ ,  $SD = 1.26$ ) cases did not report use of contraceptive medications. Demographic information is reported in Table 1.

We observed a greater proportion of missing data among athletes who did not report contraceptive use for race (36.0%) and ADHD/LD (21.2%) compared to those using contraceptives (14.5% and 0%, respectively). The proportions of missing data associated with anxiety, depression, and age were similar between groups. Groups were also similar in terms of age ( $U = 21,478$ ,  $p = 0.153$ ), race ( $X^2 = 5.154$ ,  $p = 0.397$ ), ADHD/LD diagnosis ( $X^2 = 1.920$ ,  $p = 0.383$ ), concussion history ( $X^2 = 0.185$ ,  $p = 0.667$ ), depression ( $X^2 = 0.602$ ,  $p = 0.438$ ), and anxiety ( $X^2 = 0.422$ ,  $p = 0.516$ ). As there were no differences between groups on these variables, they were not used as covariates. Days from concussion diagnosis to symptom resolution information were available for 93 cases who reported contraceptives as a medication and 284 cases who did not.

Female athletes who did or did not report contraceptive medication had similar times to symptom resolution ( $U = 14,492$ ,  $p = 0.062$ ,  $r = 0.10$ ). Figure 2 visualizes this relationship between female athletes who did or did not report contraceptive medication and symptom resolution.

### Discussion

There is a paucity of research on concussion in women. The unique features of women’s health need to be further considered to better understand sex and gender differences in recovery from concussions. Hormonal contraceptives are a factor

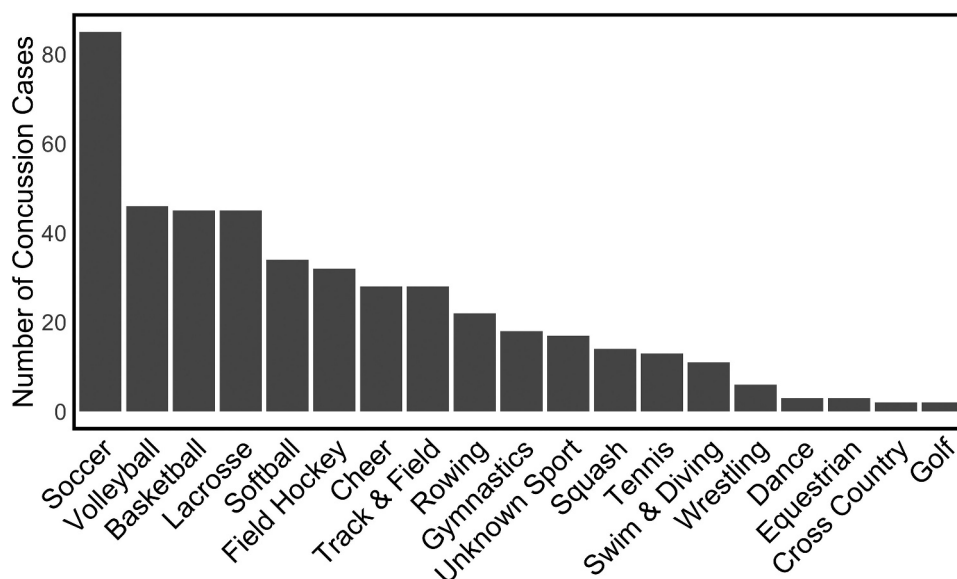


Figure 1. Female concussion cases by sport.

**Table 1.** Demographic information.

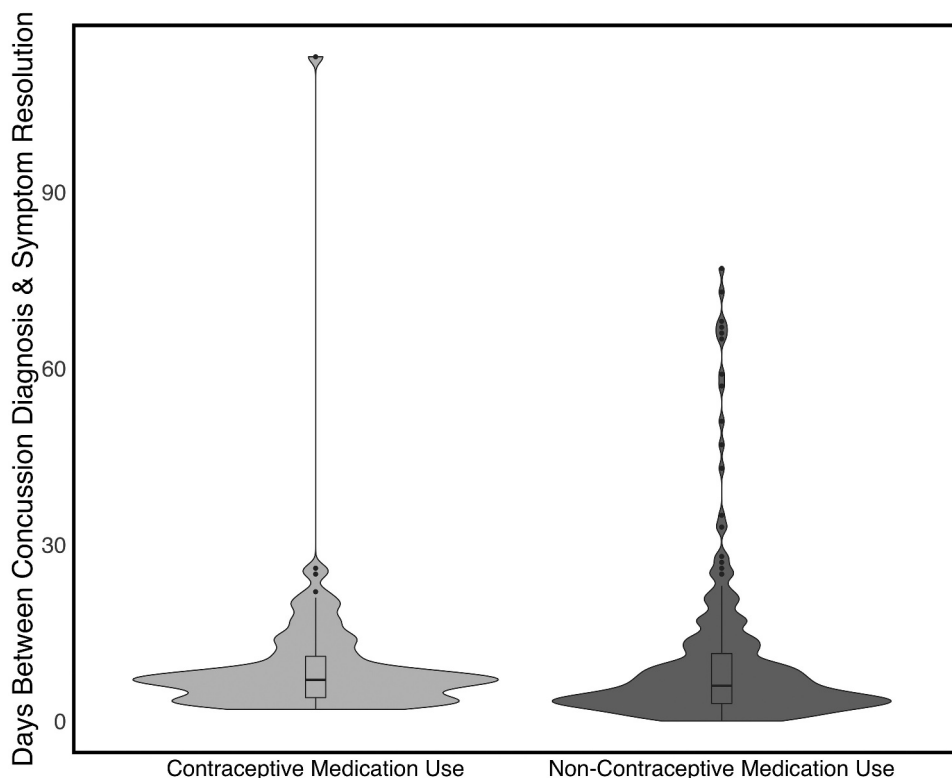
	Reported Contraceptive Medication Use ( <i>n</i> = 117)	Did Not Report Contraceptive Medication Use ( <i>n</i> = 339)
Age (median [range], IQR)	20 [17–23] years (2.0)	19 [16–23] years (2.0)
Days to symptom resolution (median [range], IQR)	7 [–1–113] days (7.0)	6 [–9–77] days (8.0)
Race/Ethnicity, <i>n</i> (%)		
American Indian or Alaska Native	0/99 (0.0%)	1/198 (0.5%)
Asian	2/99 (2.0%)	3/198 (1.5%)
Black or African American	7/99 (7.1%)	24/198 (12.1%)
Native Hawaiian or Other Pacific Islander	0/99 (0.0%)	1/198 (0.5%)
White	90/99 (90.1%)	165/198 (83.3%)
Hispanic or Latina	0/99 (0.0%)	4/198 (2.0%)
Pre-existing health conditions		
Prior Concussion, <i>n</i> (%)	48/115 (41.7%)	142/318 (44.7%)
ADHD, <i>n</i> (%)	9/117 (7.7%)	24/267 (9.0%)
Anxiety, <i>n</i> (%)	15/79 (19.0%)	33/220 (15.0%)
Depression, <i>n</i> (%)	14/87 (16.1%)	29/241 (12.0%)

ADHD/LD = Attention-Deficit/Hyperactivity Disorder and/or Learning Disorder; Information was calculated after excluding missing data for each variable; Percentages are based upon the total *n* for each contraceptive and non-contraceptive group who reported preexisting health conditions.

unique to women that may provide one physiological insight for the purported differences in concussion recovery. Our study compared the recovery of female athletes who did or did not report taking contraceptive medication. We found that female collegiate athletes had a similar number of days until symptom resolution following a concussion regardless of their self-reported contraceptive medication use. In addition, most athletes in this sample recovered within an expected timeframe of two weeks. Several considerations should be accounted for in the context of our findings.

Our findings align with previous research that did not find a relationship between contraceptive medication use and length of recovery (30,33). Similar to our study, Gallagher and colleagues (30) relied partly on retrospective medical reviews of group participants and Kay and colleagues (33)

relied on self-reported medications only at baseline. While Gallagher and colleagues (30) included data from a single site, Kay and colleagues (33) conducted a 30-site investigation. We harmonized data across 11 participating sites. None of these studies were able to measure adherence to medication or differentiate between types of oral contraceptive pills. This is an important limitation as contraceptive medications may vary in terms of the dosage of hormones, particularly progesterone. Gallagher and colleagues (30) and Kay and colleagues (33) also excluded participants with an intrauterine device (IUD) because IUDs release hormones that do not circulate throughout the bloodstream in the same concentration as taking an oral contraceptive pill (41). For this study, all contraceptive medications were considered. In addition, Kay and colleagues (33) excluded participants who were diagnosed



**Figure 2.** There were no statistical differences between symptom resolution and female athletes who reported and did not report contraceptive use as medication.



with a learning disability, developmental disorder, or mood disorder. Contrastingly, the present study included participants diagnosed with ADHD/LD, anxiety, or depression. Regardless of these differences in exclusion criteria of contraceptive medications and co-morbid diagnoses, all three studies did not identify a difference between length of recovery and hormonal contraceptives.

Exogenous increases in progesterone have been associated with improved moderate and severe TBI recovery (27,28). While the current study did not specifically study artificially elevated progesterone levels, self-reported use of contraceptive medication was used as a potential way to study progesterone given that hormonal contraceptives can introduce synthetic versions of progesterone. A possible explanation for why we did not find differences in concussion (mild TBI) recovery may be that progesterone levels play a less significant role in recovery from concussion. However, other research has demonstrated that women taking hormonal contraceptives self-report less symptoms, better quality of life, and better overall health compared to women who are not taking hormonal contraceptives both before (i.e., baseline) and after a concussion (23,30,31). This is important since acute symptom burden is a primary risk factor for recovery from concussion (3), so a lower acute symptom burden post-concussion may support improved recovery trajectory for female athletes taking hormonal contraceptives.

Objective measures of progesterone levels through blood serum or saliva have been studied in female collegiate athletes in relation to hormonal contraceptive use after a concussion and across a training season (32,42). Higher progesterone levels were associated with lower perceived stress levels after a concussion, however, the influence of the heightened progesterone on days of recovery was not assessed (32). Increased salivary progesterone in female athletes across a training season was associated with an increased blood biomarker (glial fibrillary acidic protein) that may be related to head impacts that do not result in symptoms (i.e., subconcussion) and a decrease in a blood biomarker (neurofilament light) that may play a role in protracted concussion recovery (42). Collectively, these findings suggest a positive relationship between progesterone and post-concussion outcomes, but the exact role and mechanism of action that progesterone may play in recovery from concussion has yet to be determined. Future prospective research should continue to investigate hormonal contraceptive medication as a variable factor for risk for injury as well as history when navigating individual care for concussion recovery for female collegiate athletes to confirm and extend our findings.

The current study is an important step in advancing representation of collegiate female athletes in concussion research. For example, despite women constituting 44% of all NCAA athletes, 80% of concussion research is primarily on samples of men and furthermore, 40% of concussion research does not include any women participants (43). Due to the relatively high frequency of concussions and large roster sizes in football (44), many studies include participants with concussion predominantly, and often exclusively, from football. Since there is not a collision sport for female athletes with roster sizes as large as football, much of the concussion research on female athletes represents a wider variety of sports, resulting in more heterogeneous literature. More

research with samples exclusively of women is necessary to further understand potential sex-related differences of concussion and to acknowledge that findings from concussion research on men is not inherently generalizable. In addition to improved representation in the concussion literature, future studies should continue to explore the potential impact of hormone levels on concussion recovery, with a focus on studying endogenous and injury-related hormonal fluctuations.

This study is not without limitations. The current analysis used data from the LIMBIC MATARS consortium. The clinical concussion case data were obtained from medical records of collegiate athletes from 11 participating sites. While this consortium approach allowed for a large, multi-site sample, data harmonization and missing data were a limitation. For example, multiple symptom inventories were used to evaluate acute symptom burden. Due to the varying symptom inventories through the five-year data collection period, we were unable to account for acute symptom burden between female athletes who did or did not self-report contraceptive medication use. Data was collected for contraceptive medication use at a variety of time points across consortium sites, which limits understanding of medication adherence at the time of injury. In addition, only 25.7% of our sample reported use of contraceptive medications, despite approximately 50% of elite athletes and 65% of collegiate female athletes reporting hormonal contraceptive use (29,45). This discordance is consistent with the uncertainty of self-reported contraceptive use and could also reflect current cultural concerns about women's reproductive health care rights. Self-reported data for hormonal contraceptive use is often standard, but it has notable limitations (46). It was not specified how each of the 11 sites collected this data nor can we confirm if each athlete confirmed that they were not using contraceptive medications at the time of their injury. Reliability in self-reported oral contraceptive use is improved by defining current use or patterns of use with specific language including 'continuation', 'discontinuation', 'interrupted use' and 'missed pills' (46,47). However, there is not a currently feasible, validated, and reliable method for assessing hormonal contraceptive use in the sports medicine setting. Future studies should use more objective measures of hormone levels (e.g., luteinizing hormone, follicle stimulating hormone, and progesterone) using blood serum, salivary, or urine-based measures to assess the association of hormonal contraceptive use, hormone levels, and concussion recovery.

Finally, the current findings, along with prior research on the impact of hormones in women's health, suggest that research should evolve from exclusively investigating hormonal effects on brain health and expand into other factors. This includes, but is not limited to, social determinants of health, presence or absence of healthcare professionals at the time of injury, and gender concordance/discordance (i.e., matching/not matching gender identities) of the treating healthcare provider, access to women's health specialists, and reporting patterns of concussion among women who participate in sports. Additional research is also necessary that is inclusive of different gender identities to discern how these factors as

well as hormonal contraceptive use impacts concussion recovery.

## Conclusion

Our multi-site study aimed to use a large consortium dataset to investigate the influence of contraceptive medication use on recovery from concussion in female collegiate athletes. Our results suggest that participants, regardless of contraceptive medication use, experienced symptom resolution in a similar timeframe. We believe our study is an important addition to understanding how self-reported contraceptive medication use may or may not influence recovery from sport related concussion and improves representation of women in concussion research. When interpreting the findings of this study, clinicians should consider their current documentation practices as it relates to the use of hormonal contraceptive use in women who sustain a concussion.

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