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Influence of Menstrual Cycle and Oral Contraceptive Phase on Spinal Excitability

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Abstract

Background—Rates of musculoskeletal injury differ substantially between the genders, with females more likely to experience conditions such as anterior cruciate ligament (ACL) injuries than males in the same sports. Emerging evidence suggests a significant hormonal contribution. Most research has focused solely on how hormonal fluctuations affect connective tissue, but a direct link between hormonal shifts, ligamentous laxity, and ACL injury has not been borne out. There is also evidence to suggest that sex hormones can modulate the central nervous system, but how this affects neuromuscular control is not well understood.

Objective—To determine whether changes in sex hormone concentrations would alter spinal excitability, measured across the menstrual and oral contraceptive pill cycle. We hypothesized that spinal excitability would fluctuate across the menstrual cycle (with increased excitability during the periovulatory phase due to peak estradiol concentration), but that there would be no fluctuation in oral contraceptive users.

Design—This was a prospective cohort study.

Setting—The study took place at a biomechanics laboratory at a rehabilitation hospital.

Participants—A total of 30 healthy women aged 18–35 who were similar in age, body composition, and exercise-training status were included. Fifteen of the women were eumenorrheic and nonusers of oral contraceptives (nonusers), and 15 of the women were taking oral contraceptives (users).

Main Outcome Measures—H-reflex (Hmax/Mmax ratio), serum estradiol, and progesterone concentrations were measured at 3 time points during the menstrual and contraceptive pill cycle.

Results—The H-reflex (Hmax/Mmax ratio) remained stable across the menstrual and contraceptive pill cycle. Spinal excitability was lower in the users compared with the nonusers across all testing sessions, but this was not statistically significant.

Conclusions—Our results suggest that acute fluctuations of endogenous estradiol and progesterone do not modulate spinal excitability. However, long-term exposure to exogenous estrogen and progesterone (oral contraceptives) might have an impact on spinal excitability and neuromuscular control. Further research is necessary to better understand the potential differential effect of endogenous and exogenous sex hormones on spinal excitability.

Introduction

Sexual dimorphism exists for musculoskeletal and sports-related injuries, with anterior cruciate ligament (ACL) injuries as a prime example. ACL injury rates for active females are 2–5 times greater than those for their male counterparts [1, 2]. Proposed mechanisms for this difference include anatomical, biomechanical and hormonal factors. Interest in a hormonal role is based on our evolving understanding of the pleiotropic, or multiple and varying, effects of ovarian steroids, as well as the presence of estrogen and progesterone receptors

throughout the neuromusculoskeletal system [3–5]. Whether or not gross neuromuscular control changes across the menstrual cycle remains controversial [6–10]. Two recent studies have demonstrated changes in more basic units of neuromuscular control across the menstrual cycle, particularly the activation patterns of the vastus medialis muscle [11], as well as in the muscle stretch reflex response at the rectus femoris [12]. These results support the theory that fluctuations in sex hormones modulate the basic constituents of neuromuscular control, but the exact location and mechanism of this change has yet to be determined.

We have previously demonstrated a significant decrease in the muscle stretch reflex response of the rectus femoris during the periovulatory phase of the menstrual cycle in healthy young women [12]. This finding might be secondary to changes in the structure and function of the connective tissue in the myotendinous unit [13–15]. However, the muscle stretch reflex also relies upon the function of the muscle spindle, α -motor neuron, and afferent and efferent nerve fibers. Neuromodulation by ovarian steroids has been described primarily in the brain, with estrogen having an excitatory effect and progesterone causing a reduction in neural excitability [5, 16]. If these neurosteroidal effects occur at the level of the spinal cord, then one could argue that the change that we observed in the rectus femoris muscle stretch reflex is secondary to modulation of spinal excitability. One way to evaluate changes in neuroexcitability at the spinal level in vivo is through the Hoffman reflex (H-reflex). The H-reflex is an electrically induced monosynaptic reflex arc involving the Ia-afferent fibers, homonymous α -motor neuron in the spinal cord, and efferent fibers, resulting in a twitch response of the corresponding muscle. The reflex arc is identical to the muscle stretch reflex, except that it bypasses the muscle spindle and includes only the neural component of the reflex. A low-amplitude, long-duration (1-millisecond) stimulus to the tibial nerve in the popliteal fossa preferentially stimulates the Ia-afferent fibers, resulting in a delayed motor response in the soleus, called the H-reflex (latency ~30 milliseconds). As the stimulus intensity increases, direct stimulation of the efferent fibers elicits a more rapid soleus contraction, called the M-wave (latency ~6–9 milliseconds). In clinical electrodiagnostic evaluation, the H-reflex latency is primarily used to diagnose radiculopathy. However, the ratio of the amplitude of the H-reflex to the M-wave (Hmax/Mmax) can be used in a research setting to determine the pool of available motor neurons or spinal excitability in different physiological states, including a fluctuating hormonal milieu [17, 18] (Figure 1).

Therefore, our aim was to measure spinal excitability across the menstrual and oral contraceptive pill cycle. Our hypothesis was that we would see an increase in spinal excitability during the periovulatory phase in regularly menstruating women, due to the excitatory effects of the unopposed peak in estradiol concentration before ovulation. In addition, we hypothesized that the magnitude of change would be greater in menstruating women than in women on oral contraceptives (OCs), as they should have smaller fluctuations in the endogenous sex hormonal milieu. Answers to these questions will be instrumental in our understanding of changes in neuromuscular control that seems to occur across the menstrual cycle, and, in particular, will help us to understand whether the origin of change is in the neural circuitry.

Methods

Subjects

The Northwestern University institutional review board approved our study protocol. Participants were recruited from the Northwestern University graduate campus, and written informed consent was obtained from all subjects. A total of 30 women, aged 18–35 years, volunteered to participate. These were not the same cohort of women who participated in our prior study investigating the muscle stretch reflex across the menstrual cycle [12]. The women were separated into 2 groups based on contraceptive status. Nonusers had not taken hormonal contraceptives for 12 months before testing, and they reported spontaneous menstrual cycles of 24–35 days. Users were women who had been taking a stable regimen of OCPs for at least 6 months before the testing (Table 1). Exclusion criteria included a history of musculoskeletal or orthopedic injury of the spine, hip, knee, ankle, or foot; history of neurological injury or disease of the peripheral or central nervous system; current smoking habit; history of disordered eating, stress fracture, connective tissue disorder (Marfan syndrome, Ehlers-Danlos disease), or menstrual dysfunction (primary or secondary amenorrhea, oligomenorrhea, anovulatory cycles, polycystic ovarian disease); current or prior pregnancy; starting or stopping OCPs within the previous 6 months; use of an extended-cycle oral contraceptive that eliminates a monthly withdrawal period; or use of an injectable or implantable contraceptive. We also excluded those women exercising more than 7 hours per week or participating in competitive level sports because of the high rate of undiagnosed menstrual dysfunction in females in this population [19]. Subjects were asked to maintain stable exposure to caffeine, alcohol, and exercise for 12 hours before each testing session to minimize changes in reflex excitability [20].

Experimental Protocol

Nonuser Testing Schedule—We aimed to test each nonuser once during each of the 3 key menstrual phases: follicular (low estradiol and progesterone), periovulatory (rising/peak estradiol and low progesterone), and luteal (high estrogen and progesterone; Figure 2). The classical model of the menstrual cycle was used as a reference (duration 28 days, ovulation on day 14, peak estrogen 24–48 hours before ovulation, and peak progesterone 7–10 days after ovulation) [21]. In addition, at the time of consent, each nonuser was asked to track and report the onset and duration of her menstrual cycles during the 3–4 months before data collection (day 1 was defined as the onset of menses). In addition, she was asked to use a home ovulation kit (Walgreens One Step Ovulation Predictor; Walgreens Corporation, Deerfield IL) to help anticipate the length of the follicular and luteal phases and the timing of ovulation for each subject. The information below was used to adjust the classical model of the menstrual cycle for each subject.

Nonusers who had an average of a 27- to 29-day cycle: #1 (days 1–3), testing session #2 (days 12–14), and testing session #3 (day 21–25). Nonusers who had an average of a 30- to 35-day cycle: testing session #1 (days 1–3), testing session #2 (days 14–16), and testing session #3 (days 23–27). Nonusers who had an average of a 24- to 26-day cycle: testing session #1 (days 1–3), testing session #2 (days 10–12), and testing session #3 (days 19–23).

User Testing Schedule

Users were tested in the following time frame: testing session #1 (days 1–3), testing session #2 (days 12–14), and testing session #3 (days 21–25). Day 1 for the users was defined as the first day of their withdrawal bleed.

A single investigator performed all of the testing and was blinded to subjects' menstrual cycle phase and contraceptive use. All subjects were tested 3 times. To minimize the effect of diurnal fluctuations of hormone levels, testing occurred between 7 and 9 AM for each session. Subjects were randomized to start testing in the follicular, periovulatory, or luteal phase.

Hormonal Concentrations

Venipuncture was performed by the principal investigator or in the Northwestern Medical Faculty Foundation obstetrics and gynecology outpatient laboratory. The samples were collected from the antecubital area of the subject's arm, using a 25-gauge needle and a 3.5-mL vacutainer serum separator tube (BD, Franklin Lakes, NJ). Once the tube was filled, the sample was mixed well and allowed to clot for 15 minutes. The serum was then separated by centrifugation in a Heraeus Multifuge 3S Plus (Thermo Fisher Scientific), set at 3000 rpm for 5 minutes. Estradiol and progesterone levels were analyzed using the ADVIA chemiluminescence assay. The mean percentage coefficient of variations (%CV) ranged from 4% to 12.1% (within-run) and from 4.5% to 8.1% (run-to-run) for estradiol, and from 2.5% to 12.4% (within-run) and 1.9% to 5.7% (run-to-run) for progesterone. The analysis was conducted at the Northwestern Memorial Hospital outpatient laboratory department.

Spinal Excitability

At each session, subjects were placed in a prone position on a padded examination table. The legs were positioned in hip and knee extension, with the end of the table in line with the anterior/dorsal surface of the ankle. Subjects were instructed to choose a comfortable position for their head and arms. Each subject's position was recorded, so that it could be replicated at subsequent testing sessions. The right leg was tested for all subjects and for each testing session (Figure 1). Subjects were asked to remain silent and motionless, and the testing area was quiet. This testing protocol was used in an attempt to standardize the testing environment, behavioral state, and degree of muscle activation across testing sessions, as changes in these factors can influence the H-reflex amplitude [17, 18, 22]. The intraclass correlation coefficients of the H-reflex, M-wave, and Hmax/Mmax ratio have been established and are 0.9953, 0.9514, and 0.9747, respectively [23].

Before electrode placement, the skin was cleaned and abraded with an alcohol swab. Two pre-amplified surface electromyography (sEMG) electrodes (DE-2.1 Bagnoli single differential) were placed over the muscle bellies of the soleus at the myotendinous junction (~12 cm proximal to the medial malleolus) and the peroneus longus (~5 cm distal to the fibular head) [24]. Data for the H-reflex and M-wave were recorded from the electrode on the soleus muscle. Data from the electrode on the peroneus longus muscle were monitored to ensure that there was minimal costimulation of the common peroneal nerve in the popliteal fossa. A ground electrode (Delsys Dermatode Reference Electrode, Natick, MA) was

placed between the popliteal fossa and the recording electrode. A stimulating bar bipolar electrode (Digitimer Ltd, Hertfordshire, England) was placed over the tibial nerve in the popliteal fossa, with the anode positioned distally near the popliteal crease. Optimal placement of the stimulating electrode was found by moving the stimulating electrode over the nerve until a low-current stimulus elicited the H-reflex. Once optimal placement was found, the stimulating electrode was secured to the subject with tape. The final position of the stimulus electrode was marked on the patient's skin, and the distance from the medial calcaneus to anode was measured and recorded so that it could be reproduced in future sessions. The EMG electrodes were connected to a 2-channel Delsys box (Bagnoli Handheld, 2-channel EMG system) and data acquisition hardware (National Instruments USB 6218 BNC board). Data acquisition was controlled with MATLAB software at a data acquisition rate of 2000 Hz. The level of EMG signal amplification was either 1000 or 10,000 to ensure a high signal-to-noise ratio. Stimulus intensity was controlled manually via a digitimer (DS&A constant current stimulator), and waveforms were visualized on an oscilloscope (Tektronix TDS 2014). Stimuli of 1 millisecond were delivered at 10-to 20-second intervals to prevent postactivation depression.

The H-reflex and M-wave recruitment curves were obtained by increasing the stimulus intensity in 1-mA increments starting from 2 mA, noting the peak of the H-reflex and the plateau of the M-wave [18] (Figure 3). To maximize the accuracy of these measurements, additional measurements at smaller incremental increases in stimulation intensity (0.2 mA) were obtained around the previously identified peak H-reflex. Once the stimulation intensity necessary to yield the peak H-reflex was identified, 5 measurements were obtained at a rate of 20 kHz with 10 seconds between each stimulation [25, 26] We obtained 5 measurements of the M-wave at the plateau in the same fashion.

Statistical Analyses

Analyses were conducted using PASW Statistics 18. Limited data in the literature were available for power analysis. Therefore, our power analysis to detect a group difference was based on the results from the initial 5 nonusers and users recruited for the study. Our analysis indicated that we needed 15 subjects in each group to achieve 80% power for our primary outcome. The mean and standard deviation were calculated for subject characteristics. To analyze the demographic difference between users and nonusers, 2-tailed independent-samples *t* tests were used. The significance of 2-tailed tests was set at $P < .05$. A series of 2 (group: users versus nonusers) $\times$ 3 (time: menstrual and contraception cycle phase: follicular, ovulatory, and luteal) mixed-model analyses of variance were conducted as the primary analyses. The following assumptions were tested: independence of observations, normality, and sphericity. Independence of observation and sphericity were met. The assumption of normality was violated for some the variables (estrogen and progesterone levels), which were transformed. All transformations yielded normal distributions. For secondary analyses, a 2 $\times$ 3 analysis of variance (ANOVA) was conducted to evaluate the consistency of the maximal M-wave values across the 3 sessions for both groups. A Pearson correlation was conducted to assess the relationship between Hmax/Mmax ratio and estrogen.

Results

A total of 30 women participated in the study, 15 nonusers and 15 users. There were no significant differences between the groups with respect to age (nonusers 23.0 ± 3.0 years, users 25.0 ± 3.0 years, $P = .10$) or body mass index (nonusers 23.5 ± 3.4 kg/m², users 24.0 ± 2.7 kg/m², $P = .67$). The users had been taking their respective contraceptive for an average of 36 months (Table 1 provides information on specific contraceptives used).

Primary Analyses

The means and standard deviations for the Hmax/Mmax ratio of the 2 groups by phase of cycle are presented in Table 2 and Figure 3. A 2×3 ANOVA was conducted to evaluate these variables over the course of the menstrual cycle among OCP users and nonusers. The Hmax/Mmax ratio was lower in the users compared to the nonusers in all phases, but the ANOVA examining Hmax/Mmax ratio yielded no significant interaction ($F_{2,56} = 0.671$, $P = .515$, partial $\eta^2 = 0.023$) or main effects for group ($F_{1,28} = 2.748$, $P = .109$, partial $\eta^2 = 0.089$) or phase in the cycle ($F_{2,56} = 0.742$, $P = .481$, partial $\eta^2 = 0.026$).

Secondary Analyses

Descriptive information for estrogen and progesterone concentrations by group and cycle phase is presented in Table 3. Mixed-model ANOVAs were conducted to examine estrogen and progesterone levels over the menstrual/contraceptive pill cycle. Results examining estradiol concentration indicated that the main effects of phase of cycle and group were significant ($F_{2,56} = 9.523$, $P < .001$, partial $\eta^2 = 0.254$, and $F_{1,28} = 1391.949$, $P < .001$, partial $\eta^2 = 0.589$, respectively). The Phase $\times$ Group interaction effect was also significant ($F_{2,56} = 23.867$, $P < .001$, partial $\eta^2 = 0.460$), indicating that the pattern of responses is different for those users compared to nonusers of OCPs. Pairwise comparisons with Bonferroni correction were used to follow up on the significant interaction effect. The users had an increase in estradiol concentration during the phase that corresponded with ovulation in the nonusers (mean difference = 0.217, $P = .009$); whereas the nonusers had significant increases in estradiol concentration from the follicular phase to the ovulatory phase ($P < .001$) and from the follicular phase to the luteal phase ($P < .001$). There was a minimal, nonsignificant decrease from the ovulatory to the luteal phase.

Results examining progesterone concentration indicated that both the phase and group main effects were significant ($F_{2,56} = 12.506$, $P < .001$, partial $\eta^2 = 0.309$, and $F_{1,28} = 27.068$, $P < .001$, partial $\eta^2 = 0.492$, respectively). The phase $\times$ group interaction effect was also significant ($F_{2,56} = 13.241$, $P < .001$, partial $\eta^2 = 0.321$), indicating that the pattern of progesterone concentration is different for users of OCPs compared with nonusers. The significant interaction was followed-up with pairwise comparisons, which showed that the users had stable levels over the menstrual cycle with no significant changes, whereas nonusers showed increases over the cycle with a significantly higher level during the luteal than either the follicular ($P < .001$) or ovulatory ($P < .001$) phase.

Pearson correlations examining the relationship between Hmax/Mmax ratio and estrogen as well as progesterone were not statistically significant.

To ensure that we were testing a similar muscle contraction across the menstrual cycle, we analyze the maximum M-wave and found that it was consistent across the menstrual cycle ($F_{2,56} = 0.320$, $P = .727$).

Discussion

The purpose of this study was to determine whether spinal excitability is modulated by fluctuating sex hormones throughout the menstrual cycle. Our primary hypothesis was that spinal excitability would be increased with peak estradiol concentration in the periovulatory phase. This hypothesis was based on the knowledge that ovarian hormones play a modulatory role in brain excitability [5, 27], and that estrogen and progesterone modify the output of respiratory motor neurons in rodents [28, 29]. To our knowledge, there have been only 2 prior studies that have investigated the effect of gonadal steroids on spinal excitability [30, 31]. Hoffman et al studied regularly menstruating women with a control group of men [30]. The investigators measured the Hmax/Mmax ratio and urinary estrogen and progesterone across the menstrual cycle. They found no relationship between the hormonal concentrations and the Hmax/Mmax ratio. However, urine has been shown to be less sensitive than serum to fluctuations in sex hormones across the menstrual cycle in regard to the magnitude of change, and there is a 1-day lag in urinary concentrations compared to serum hormonal peaks [32]. Bonifazi et al measured cortical and spinal excitability in males who received a single injection of hCG to create an experimental model of transiently elevated estradiol and testosterone [31]. The fact that the Hmax/Mmax ratio remained stable in this study suggests that an acute increase in serum estrogen does not alter spinal excitability in males, but it does not address any potential female-specific response, nor does this study address any potential role of progesterone. In light of these results, we aimed to create a gender-specific model using serum levels of hormonal fluctuations with a group of nonusers and users of OCPs. Our results are consistent with the 2 prior studies in that spinal excitability did not change with acute fluctuations in endogenous estrogen or progesterone. One interpretation of these collective findings is that the change that we previously observed in the muscle stretch reflex across the menstrual cycle may not be attributable to changes in spinal excitability [12]; yet there are some additional factors to consider before coming to this conclusion.

One important consideration is that the H-reflex might not have enough resolution to detect a small change in spinal excitability. Even though the H-reflex is considered to be the primary probe for noninvasive study of sensorimotor integration of the central nervous system in humans [17], it is not a direct measure of the motor neuron. Thus the sensitivity may not be adequate to measure changes in excitability as a result shifting sex hormone concentrations. However, there are examples in which the H-reflex has been sensitive enough to demonstrate an acute change after administration of other substances such as caffeine [33] and selective serotonin reuptake inhibitors [34], so we would expect that this same model should work in the setting of the menstrual cycle. Furthermore, although the H-reflex is the electrical analogue to the monosynaptic muscle stretch reflex, it is clear that H-reflex amplitude is affected to some degree by pre- and postsynaptic events [17]. It is likely that the only way to differentiate whether the change in spinal excitability is occurring

proximal to or at the level of the motor neuron is to use an animal model with direct examination of the state of the motor neuron in response to acute change in sex hormones.

An additional area for consideration is our limited testing paradigm targeting the 3 main phases of the menstrual cycle. Although this method has been used frequently in prior literature [21], it may have resulted in missing a significant change in the H-reflex or interaction between spinal excitability and hormonal concentrations. For example, if a subject's follicular phase was shorter or longer than expected, then we may have missed the true peak of estradiol. Furthermore, lack of daily testing could result in missing the time delay that may occur with hormonal fluctuations and the subsequent change in spinal excitability, similar to the 4-day lag time in changes in ligamentous laxity described by Shultz et al [35]. In addition, using a range of days (ie, luteal testing performed at some point between days 21 and 25) as well as the large intersubject variability in phase duration and concentrations of sex hormones may have limited our ability to detect actual change in spinal excitability [36]. One final limiting factor in our ability to couple these findings with our prior work on the muscle stretch reflex is that we did not conduct this testing at the same time and on the same cohort of women [12]. Thus, we cannot definitively state that the change that we previously observed in the muscle stretch reflex is not due to changes in spinal excitability.

Our secondary hypothesis was that the nonusers of OCPs would display greater fluctuations in spinal excitability than the users; however, we did not find any significant changes in spinal excitability in either group. To our knowledge, this is the first time that the H-reflex has been evaluated across the contraceptive pill cycle. We chose this as our comparative group because we previously demonstrated that nonusers of OCPs have a greater decrease in the muscle stretch reflex of the rectus femoris during the peri-ovulatory phase than users [12]. We hypothesized that the elevated levels of estradiol in nonusers would enhance spinal excitability, but that the users would have stable hormonal concentrations and spinal excitability. Our hypothesis was based on the fact that the exogenous hormones in the OCPs result in negative feedback to the hypothal–amicepituitary–ovarian axis, resulting in low stable concentrations of endogenous estrogen and progesterone [37]. However, our results show that OCPs do not mitigate cyclic changes in sex hormones, as the users demonstrated a trend similar to that in the nonusers, with a significantly higher peak of endogenous estradiol during the second testing session. This knowledge is critical to interpreting our data and other studies involving women on OCPs, because both sets of women demonstrated fluctuations in estrogen across the menstrual and contraceptive pill cycle, but the users are also being exposed to exogenous hormones that were not measured with the assays used in this study. Interestingly, there was a trend toward a lower spinal excitability in users compared to nonusers at each of the testing sessions. Although the underlying mechanism for this potential difference is not entirely clear, it is possible that chronic exposure to the exogenous progesterone in OCPs may downregulate neuronal excitability in the central nervous system [38]. If this is the case, one would expect that the level of downregulation might relate to the type of pill, particularly the potency and androgenicity of the synthetic progesterone within the respective OCP (Table 1). As we did not have an adequate sample size to answer this question, and as we did not control for equal numbers of woman taking various types of OCPs, we were unable to fully evaluate this relationship. This concept of

the differential effect of exogenous and endogenous sex hormones has been explored in a variety of other musculoskeletal tissues. OCPs have been shown to have potentially advantageous effects in regard to sports injury, including decreased ACL laxity [39], increased Achilles tendon stiffness [40], and less muscle damage in response to eccentric exercise [41]. On the contrary, OCPs have been shown to have some negative effects such as greater inhibition of exercise-induced collagen synthesis in tendons [42] and protein synthesis in muscle [43]. Furthermore, it has been suggested that OCPs might modulate injury risk; however, this idea remains controversial, due to a lack of understanding of the true effect of exogenous estrogen and progesterone on the neuromusculoskeletal system. The idea that chronic exposure to OCPs might influence spinal excitability warrants further investigation, as more than 10 million women in the United States and 100 million women worldwide report taking OCPs [44, 45].

Future directions include addressing the limitation of our study and including more functional measures of neuromuscular control. The 2 major limitation of our study are the limited sampling at 3 time points and the use of an indirect measure of spinal excitability. It is possible that we did not test each subject within the desired phase of the menstrual cycle, and that a more frequent, ideally daily, testing paradigm should be conducted in future studies. Furthermore, this line of investigation should include a direct measure of motor neuron excitability, which is most feasible in an animal model to avoid the pitfalls that occur with using H-reflex as a proxy for spinal excitability. Finally, sex hormones may participate in a complex interaction with other hormones and neurotransmitters, such as relaxin [46], glutamate, and γ -aminobutyric acid [5], so a more comprehensive hormonal analysis should be conducted. In addition, future investigation should include simultaneous muscle stretch reflex, H-reflex, and functional testing of neuromuscular control across the menstrual cycle to help bridge the gap between mechanistic studies and clinically relevant findings that might help with injury prevention strategies. Our hope is that this type of exploration would lead to risk reduction strategies for sports-related injury, but might also be translated to other significant musculoskeletal problems that seem to have a hormonal component, including knee osteoarthritis and pregnancy-related lumbopelvic pain [47–49].

Conclusion

This study adds important information to our current understanding of the relationship between neuromuscular control and endogenous sex hormones. Our results support the findings of Hoffman et al that spinal excitability remains stable across the menstrual cycle. However, because of limitations in using the calendar method for testing and for using a cohort of women different from the one that we studied previously, we cannot confidently state that the attenuation of the muscle stretch reflex during the periovulatory phase of the menstrual cycle is not the result of a change in spinal excitability. Further investigation in this area, including using a daily testing paradigm to identify potential time-delayed changes in motor neuron function in response to hormonal shifts, and simultaneous monitoring of the muscle stretch reflex and the H-reflex, are necessary to definitively determine the location of our observed change. In addition, our results add novel information regarding the potential of a differential effect of endogenous and exogenous estrogen and progesterone on spinal

excitability. Because of the the extensive use of OCPs, a thorough understanding of their effects throughout the neuromusculoskeletal system is critical.

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Figure 1. H-reflex testing. **(A)** Patient in the prone position. **(B)** Sample H-reflex and M-wave. **(C)** Sample recruitment curve demonstrating the peak H-reflex and M-wave plateau.

Figure 2.

Sample testing schedule for a nonuser with menstrual cycle duration of 27–29 days: follicular testing (days 1–3), periovulatory testing (days 12–14), and luteal testing (days 20–24). Users were tested at similar time points. Day 1 was defined as the onset of menses (nonusers) or withdrawal bleed (users). Reprinted with permission from Medicine & Science in Sports & Exercise.

Figure 3.
Hmax/Mmax ratio for nonusers and users during the menstrual and contraceptive pill cycle.

Table 1

Profile of oral contraceptives in the user group

No. of Subjects	Trade Name	Type	Ethinyl Estradiol Dose (mg)	Progestin	Progestin Dose (mg)	Potency*	Androgenicity*
2	Ocella	Mono	0.030	Drospirenone	3.000	4.500	0.000
2	Yasmin	Mono	0.030	Drospirenone	3.000	4.500	0.000
1	Zarah	Mono	0.030	Drospirenone	3.000	4.500	0.000
1	Microgestin 1.5/30	Mono	0.030	Norethindrone	1.500	1.500	1.500
1	Kariva	Mono	0.020	Desogestrel	0.150	1.350	0.510
3	Junel Fe	Mono	0.030	Norethindrone	1.000	1.000	1.000
1	LoLoestrin Fe	Mono	0.010	Norethindrone	1.000	1.000	1.000
1	Zenchant Fe	Mono	0.035	Norethindrone	0.400	0.400	0.400
1	Lutera	Mono	0.020	Levonorgestrel	0.100	0.530	0.830
1	Ortho-tricyclen Lo	Tri	0.025	Norgestimate	0.180	0.234	0.342
					0.215	0.280	0.409
					0.250	0.325	0.475
1	Trinessa Tab	Tri	0.035	Norgestimate	0.180	0.234	0.342
					0.215	0.280	0.409
					0.250	0.325	0.475

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* Relative to 1-mg dose of norethindrone.

Table 2
Mean values and standard deviation for Hmax/Mmax ratio by group and phase in the menstrual cycle

Hmax/Mmax ratio	All Subjects		Users		Nonusers	
	Mean	SD	Mean	SD	Mean	SD
Follicular	0.5647	0.212	0.5063	0.209	0.6231	0.205
Ovulatory	0.5454	0.214	0.4767	0.176	0.6141	0.232
Luteal	0.5288	0.192	0.4935	0.181	0.5642	0.203
Average	0.5463	0.204	0.4922	0.185	0.6005	0.210

SD = standard deviation.

Table 3

Mean values for standard deviation for Hmax/Mmax ratio by group and phase in the menstrual cycle

	<u>Users</u>		<u>Nonusers</u>	
	Mean	SD	Mean	SD
Estradiol				
Follicular	37.440	28.469	42.277	16.269
Ovulatory	54.520 *	99.820	203.855 *	135.010
Luteal	20.759	10.280	153.233 *	92.794
Progesterone				
Follicular	0.327	0.181	0.499	0.236
Ovulatory	0.307	0.172	0.714	0.463
Luteal	0.314	0.159	6.857 *	4.806

SD = standard deviation.

* Significantly different from follicular phase.