Standing balance is not affected by estrogen fluctuations during the menstrual cycle

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Abstract

Even when standing still, people unconsciously shift their body's center of mass. These shifts can be recorded to compute a metric called postural sway; higher levels of sway are associated with "worse" balance and greater fall-risk in some populations. Women and men exhibit different levels of postural sway. In general women show less sway than men, but this difference only begins to appear around puberty, pointing to different levels of sex hormones in men and women as one potential mechanism for sway sex differences. In eumenorrheic people, sex hormones fluctuate over the menstrual cycle, so it is possible that balance would change over the course of the cycle as well. Previous studies have examined the relationship between the menstrual cycle and balance and reported conflicting findings. However, those studies used small cohorts and generally did not measure sex hormone levels. In this study, we measured estrogen (estradiol) levels and postural sway during 4 timepoints over the menstrual cycle in two larger cohorts of women, some using oral contraceptives and some eumenorrheic. We found no effect of the menstrual cycle or absolute levels of estradiol on postural sway.

Introduction

Estrogen plays a variety of roles in extragonadal tissues. In addition to its wide-ranging effects on bone (Cutler, 1997; Kalervo Väänänen & Härkönen, 1996; Riggs, 2000), estrogen plays a role in the formation, maintenance, and function of muscle, connective tissue, and a variety of other structures including the brain (Chidi-Ogbolu & Baar, 2019; Cui et al., 2013; Hansen, 2018; Leblanc et al., 2017). During the menstrual cycle estrogen levels can vary from under 15 to over 400 pg/mL (Buchanan et al., 1986; Denver et al., 2019) in eumenorrheic women, whereas estrogen levels tend to be well under 100 pg/mL in men (Khosla et al., 2001). Despite these regular fluctuations in estrogen levels and estrogen's widespread effects, it remains unclear whether estrogen availability affects motor behaviors.

One important motor ability is balance, or our ability to maintain an upright posture without falling over. Balance is an intriguing place to look for estrogen related fluctuations because there are sex differences in some behavioral measures related to balance function. One of these measures, postural sway, is consistently lower in women compared to men, but this difference does not appear until around puberty and is not accounted for by other likely covariates like height or weight (Goble & Baweja, 2018a, 2018b; Moran et al., 2020). Postural sway is a measure of spontaneous shifts of a person's center of mass as they stand stationary. While postural sway is not the same as balance and may reflect multiple neural processes (Carpenter et al., 2010; Latash & Zatsiorsky, 2016; Mochizuki et al., 2006), it is often interpreted as related to balance in that people who show more postural sway are considered to have worse balance and be more likely to fall (Fernie et al., 1982; Johansson et al., 2017).

Balance depends on both sensory and motor factors (Mancini & Horak, 2011; Shumway-Cook & Horak, 1986). While many sensory systems are involved in balance, sensation from the bottom of the foot and from proprioceptors in ankles are implicated in age-related changes in postural sway (Anson et al., 2017; Fridén et al., 2003; Goble et al., 2011). Estrogen affects connective tissues including tendon and ligament, which in turn could alter the relationship between muscles and proprioceptors. Estrogen can alter the structural properties of connective tissues by changing the amount of collagen incorporated into them, the formation of collagen-elastin crossbridge structures, and can also alter connective tissue metabolism (Chidi-Ogbolu & Baar, 2019; Hansen, 2018; Leblanc et al., 2017). While these changes could affect the mechanical connections between proprioceptors and muscles, there is not a strong consensus on these findings *in vivo* in humans. While one group has consistently indicated changes in connective tissue and muscle properties over the menstrual cycle (Lee et al., 2013; Petrofsky & Lee, 2015; Yim et al., 2018), others have reported no functional changes on that timescale (Bryant et al., 2008; Burgess et al., 2009; Ericksen & Gribble, 2012; Kubo et al., 2009).

A number of studies have reported that postural control changes over the course of the menstrual cycle (Darlington et al., 2001; Maged et al., 2017; Mokošáková et al., 2018; Petrofsky & Lee, 2015; Sung & Kim, 2018; but see Ericksen & Gribble, 2012), generally reporting decreases in balance-related measures with higher levels of estrogen. In conjunction with observations about the timing and prevalence of certain knee and ankle injuries (Wojtys et al., 2002), these findings have been interpreted as indicative of increased injury risk and been taken

as evidence supporting the prophylactic use of oral contraceptives to decrease musculoskeletal injury risk in eumenorrheic people. Given the seriousness of these interpretations, it is important to note that the existing literature has tended to use very small participant cohorts, difficult-to-replicate balance measures, and rarely directly measured hormone levels. Here we address these concerns by measuring both postural sway and hormone levels four times over the course of the menstrual cycle in a fairly large cohort of eumenorrheic young women as well as another cohort of young women taking oral contraceptives. We find no differences in postural sway over the course of the menstrual cycle or between the two cohorts, and no evidence of an association between hormone level and postural sway across participants.

Materials and Methods

Participants

We recruited healthy young women who were either eumenorrheic or using oral contraceptives to participate in this study. These women were part of a larger study investigating the effects of oral contraceptives on bone health. Participants were required to be between 18-25 years old, have a BMI between 18-32 kg/m^2, be non-smoking, consume fewer than 2 alcoholic drinks per day and not be pregnant or lactating. Participants using oral contraceptives had been using them for at least one year and no more than 5 years; individuals using other forms of hormonal contraceptives were not eligible to participate. Eumenorrheic participants had not been using hormonal contraceptives for at least 3 months before they participated. We conducted this study in accordance with procedures approved by the San Diego State Institutional Review Board's Human Research Protection Program. In total, we report results from 78 women; 60 women completed four sets of blood draws; 72 completed four sets of balance tests, and 54 of the women in those cohorts completed full sets of both testing protocols. Physical characteristics of the participants in each sample are provided in table 1.

Table 1. Physical characteristics of participants

	N	*Age (SD) yr*	*Height (SD) cm*	*Weight (SD) kg*
Complete estradiol data (N = 60)				
Eumenorrheic	26	21.7 (2.0)	161.6 (6.1)	61.1 (12.2)
Oral Contraceptive	34	21.2 (1.8)	163.6 (5.68)	60.6 (7.6)
Complete balance data (N = 72)				
Eumenorrheic	30	21.3 (1.9)	162.2 (6.1)	63.0 (12.5)
Oral Contraceptive	42	21.2 (1.6)	163.0 (6.0)	59.5 (8.02)
Complete balance + estradiol data (N = 54)				
Eumenorrheic	26	21.7 (2.0)	161.6 (6.1)	61.1 (12.2)
Oral Contraceptive	28	21.3 (1.7)	163.8 (6.3)	61.1 (8.3)

Testing protocol and quantifying menstrual cycle

We scheduled each participant to make four visits for blood draw and balance testing. For eumenorrheic participants, these visits corresponded to menstrual cycle days 1,4,11, and 21

(first day of follicular phase, early follicular phase, ovulation, and mid luteal phase, respectively). For participants using oral contraceptives, these visits corresponded to pill pack days 21 (start of placebo pills), 24, 3, and 13 (intervals between visits corresponding to eumenorrheic visits days 4, 11, and 21). We asked participants to fast for 10 hours before their scheduled visits and we instructed oral contraceptive users who consumed their pill in the morning to wait until after the blood draws. We centrifuged samples immediately after blood draws for 15 minutes at 4000 x *g* at 4° C and subsequently stored the samples at -80° C until analysis.

Evaluating balance

We evaluated participants' balance using the BtrackS Balance Test (BBT; Balance Track Systems, Inc. San Diego, CA, USA). The BtrackS system incorporates a standardized low-cost force plate and data collection protocol to quantify postural sway during quiet standing. Postural sway results from the natural, spontaneous motion of a person's center of mass as they stand "still" and reflects the combination of neural outputs and sensory inputs that govern balance. Balance is inversely related to postural sway: a person who displays more postural sway (meaning their center of mass moves more) is considered to have worse balance.

The BBT testing protocol involves recording postural sway during three, 20 s trials following one familiarization trial. During these trials, participants are instructed to stand as still as possible on the BtrackS force plate with their eyes closed and feet shoulder width apart. The BtrackS force plate records the center of pressure (the projection of the center of mass onto the ground) at a rate of 25 Hz. Results from the BBT have been validated against laboratory-quality force plates (Goble et al., 2018; O'Connor et al., 2016; Richmond et al., 2018). The outcome measure of the BBT ("BBT Score") is the average length, in cm, of the path the COP covers during the 3 trials. While the precise link between balance and postural sway is unknown (Latash & Zatsiorsky, 2016), extensive normative data is available for comparing BBT scores.

Measuring estradiol

We measured estradiol (E_2), which is the most biologically active and most prevalent form of estrogen. We analyzed the level of estradiol in plasma in each sample using ultra-sensitive estradiol ELISA kits (ALPCO, Salem, NH, USA). These ultra-sensitive ELISA kits have a sensitivity of 1.399 pg/mL with a range of up to 200 pg/mL. For samples that exceeded the upper limit of the ultra-sensitive ELISA kits, we then used standard ELISA kits (ALPCO, Salem, NH, USA) which have a sensitivity of 10 pg/mL with a range of up to 3200 pg/mL.

Statistics

To test the effect of the menstrual cycle and oral contraceptive use on estradiol levels, we used a two-way repeated measures ANOVA with the factors Visit (4 levels, corresponding to when participants visited the lab during the menstrual cycle) and Contraceptive status (two levels corresponding to whether that participant was using oral contraceptives or eumenorrheic) on the response variable of estradiol level. We log-transformed estradiol level for normality, as assessed visually via QQ-plots. We used a repeated-measures ANOVA with the same factors and the response variable BBT score to assess the effect of the menstrual cycle and oral

contraceptive use on static balance (postural sway). When p-values were greater than the arbitrary level of significance $\alpha = 0.05$, we also report Bayes Factors (BF_{10}) for additional interpretive value. Unlike large P-values, small Bayes Factors can be interpreted as evidence for the null hypothesis (Kass & Raftery, 1995). The aforementioned ANOVAs use day of menstrual cycle as a proxy for estradiol level, we directly investigate whether there was an association between estradiol level and balance by correlating estradiol level and BBT score for the participants who had completed both tests during all four visits.

We used the programming language and environment R (version 4.2.0, R Core Team, 2022) to perform our frequentist statistical analyses. When analyzing multiple factors with multiple levels, we used two-way repeated-measures ANOVA. We implemented these ANOVAs using linear mixed-model analysis with reduced maximum likelihood fitting (*lme4* package; Bates et al., 2014) with independent intercepts (but not independent slopes), and treating individual participants as random factors. We obtained p-values for effects with the Kenward-Roger approximation for denominator degrees of freedom, implemented via *lmerTest* (Kuznetsova et al., 2017) and *pbkrtest* (Halekoh & Højsgaard, 2014) packages and used *emmeans* (Lenth et al., 2022) for post-hoc comparisons. We performed the same analyses in a Bayesian framework using JASP (version 0.16.3, JASP Team, 2022) with the Bayesian ANOVA workflow treating individual participants as random factors and default assumptions. We performed correlations using the *pearsonr* command in the *Scipy* library (Virtanen et al., 2020) for Python.

Results

Oral contraceptive use is linked to decreased estradiol levels

This study investigated the effect of estrogen on postural sway, which is related to balance, in a cohort of young women using oral contraceptives (N = 34) and a second, eumenorrheic cohort (N = 26). We observed a large range of estradiol levels in both groups: across all visits and participants, estradiol levels in young women using oral contraceptives ranged from 0.1 pg/mL to 1317.7 pg/mL; in eumenorrheic young women, estradiol levels ranged from 5.4 pg/mL to 1548.6 pg/mL. These levels and group averages are similar to those reported in previous studies (Bryant et al., 2008; Buchanan et al., 1986; Denver et al., 2019).

First we performed statistical analysis to establish that oral contraceptives altered estradiol concentration (log-transformed for normality) across the menstrual cycle. We used a two-way repeated-measures ANOVA to investigate the effect of oral contraceptive use and day of the menstrual cycle on estradiol level. We found a significant interaction between day of menstrual cycle and oral contraceptive use ($F_{3,174} = 12.83$; $P = 1.29e^{-7}$). Post-hoc comparisons show that estradiol levels were lower in the group using oral contraceptives during days 11 and 21. Estradiol levels did not vary significantly over the course of the menstrual cycle for women using oral contraceptives. For eumenorrheic participants, estradiol levels were higher during days 11 and 21 than days 1 and 4, but the levels between the first two and second two visits were not significantly different. These results are shown in Figure 1.

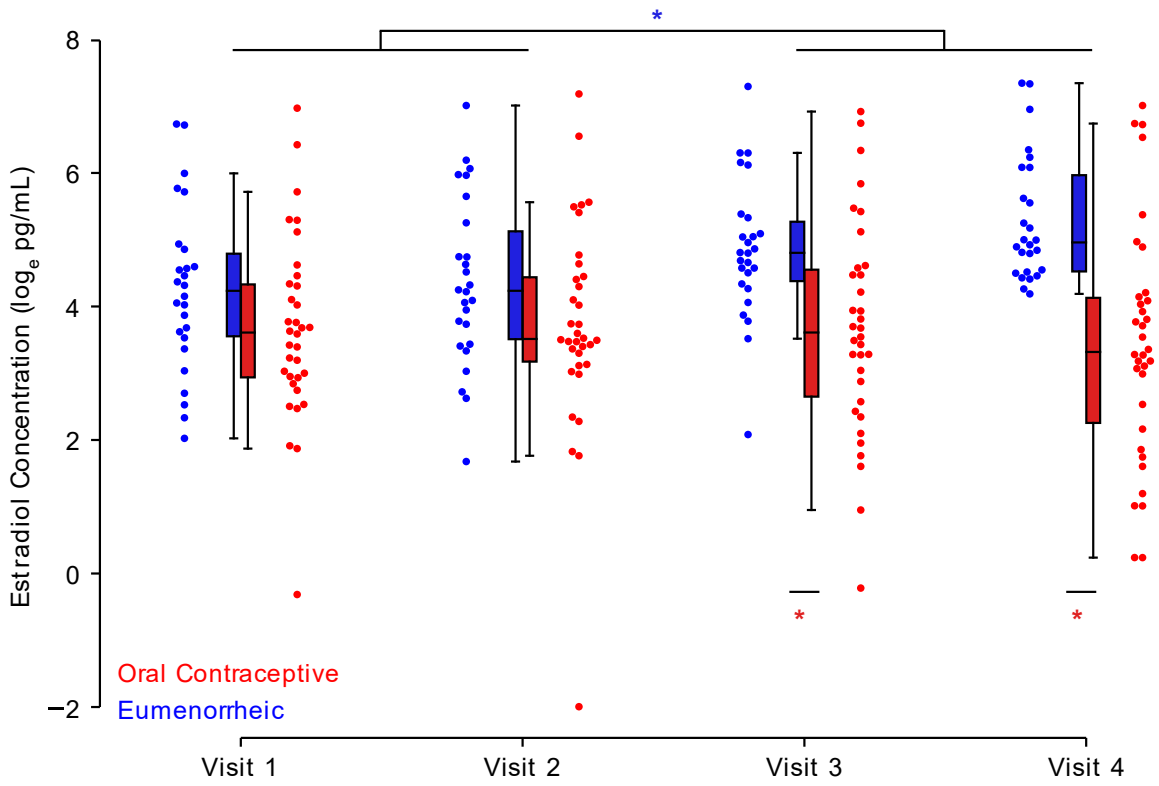

Figure 1: Estradiol concentration. Plasma estradiol concentration as measured via blood draw in young women taking oral contraceptives (n = 34; blue) and in eumenorrheic young women (n = 26; red). In the cohort on oral contraceptives, visits 1-4 correspond to days 21, 24, 3, and 13, respectively, on their pill packs. In the cohort not taking oral contraceptives, visits 1-4 correspond to days 1, 4, 11, and 21 of the menstrual cycle. Red asterisks indicate significant differences between oral contraceptive and eumenorrheic groups; blue asterisk indicates differences in the eumenorrheic group at different timepoints.

Postural sway is unaffected by menstrual cycle

We next investigated whether postural sway varied over the course of the menstrual cycle for women who were using oral contraceptives (N = 42) and eumenorrheic women (N = 30). Across days and participants, we observed a range of pathlengths from 13.82 cm to 48.47 cm in the women using oral contraceptives and from 13.81 cm to 36.59 cm in eumenorrheic women.

On average, postural sway was higher for women using oral contraceptives (23.48, 24.09, 23.17, and 23.12 cm for visits 1-4, respectively) than eumenorrheic women (22.44, 21.41, 22.28, and 21.56 cm for visits 1-4) at every visit. Compared to previously published normative data using this postural sway paradigm, all of these values are between the 30th and 50th percentiles for women ages 15-29 (Goble & Baweja 2018). Figure 2 shows the average values and all individual participants' data, which gives the visual impression that the variability of the data is high compared to mean differences, and the magnitude of the differences is lower than the minimum meaningful difference for this test (5cm; Goble et al. 2016). We again used a two-way repeated-measures ANOVA to investigate the effect of day of the menstrual cycle and contraceptive use on postural sway. This analysis did not show any significant effect of day of

the menstrual cycle ($F_{3,210} = 0.19$; $P > 0.9$; $BF_{10} = 0.02$) or of contraceptive use ($F_{1,70} = 0.97$; $P > 0.3$; $BF_{10} = 0.62$), without significant interaction.

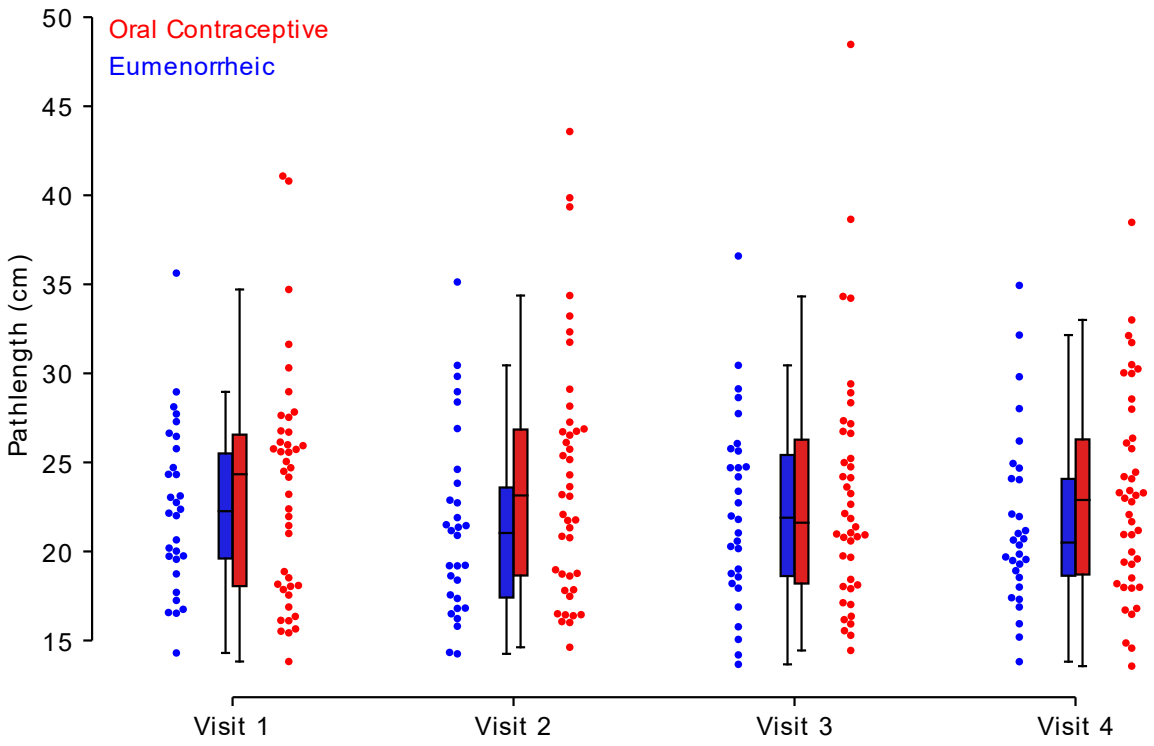

Figure 2: Postural Sway Pathlength for each visit. Postural sway quantified as the average pathlength over 3 eyes-closed quiet standing trials for 20 s each. Blue dots represent an individual's data in the group using oral contraceptives (n = 42) and red dots represent data for eumenorrheic individuals (n = 30).

Estradiol level is minimally associated with postural sway

We analyzed the effect of the day of the menstrual cycle on estradiol level and separately on balance in overlapping cohorts. However, not all participants who had a full set of blood tests also had a full set of balance tests. Given the heterogeneity of estradiol levels between individuals and across the menstrual cycle, and that our research question was about the relationship between estrogen level and balance, we directly tested whether estrogen level was associated with postural sway using correlation analyses. For 54 participants with complete balance and blood tests (28 using oral contraceptives and 26 eumenorrheic participants), we correlated estradiol level with postural sway (Figure 3). The correlation between estradiol concentration and postural sway was not significant for women using oral contraceptives ($r = 0.12$; $P = 0.21$), nor was it significant for eumenorrheic women ($r = 0.15$; $P = 0.13$). These data are shown in Figure 3.

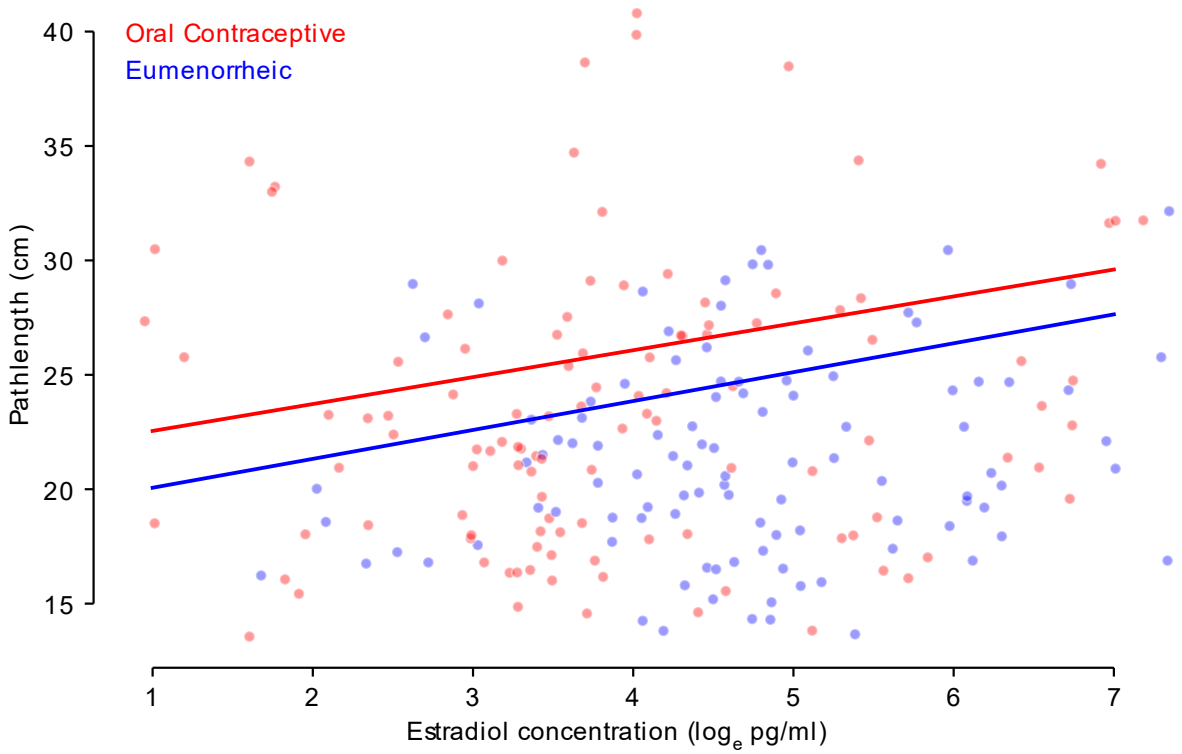

Figure 3: Correlation of estradiol and postural sway. Scatterplot showing postural sway (pathlength) and estradiol concentration (log-transformed for visualization) in participants who completed both blood draw and balance testing during all four visits. Participants using oral contraceptives (n = 28) are blue and those not using oral contraceptives (n = 26) are red. Correlations between postural sway and estradiol were not significant in either cohort. Solid lines represent linear best-fits; the slope of each line is equal to the correlation coefficient.

Discussion

Our eumenorrheic participants showed robust changes in estradiol levels during the course of the menstrual cycle. However, our measures of balance do not support the idea that postural sway changes over the course of the menstrual cycle (and $BF_{10} = 0.02$ is often interpreted as moderate to strong evidence for the null hypotheses, e.g. no differences due to menstrual cycle fluctuations). On average, participants using oral contraceptives (who had lower levels of estradiol) showed larger amounts of postural sway than eumenorrheic participants, but these differences are not statistically significant (and $BF_{10} = 0.6$ is often interpreted as weak evidence for the null hypothesis). When we compared estradiol levels to participant sway across all participants, we found no evidence that varying levels of estradiol affect postural sway in people using oral contraceptives.

Previous association of balance and hormone levels

Previous studies report conflicting findings about whether balance-related measures change over the course of the menstrual cycle. Some groups have reported changes in balance over the course of the menstrual cycle during “more challenging” tests, for example eyes closed in

combination with unstable surfaces and tandem foot position in which one foot is in front of the other (Petrofsky & Lee, 2015). While it is possible we would have seen differences if we had used other balance-related testing protocols, there are also studies that report changes in balance metrics using methods that are similar to those we used (eyes closed and standing on a firm surface) over the course of the menstrual cycle (Mokošáková et al., 2018), as well as studies that do not report changes using dynamic balance tasks (Ericksen & Gribble, 2012).

When studies find a difference in balance metrics over the course of the menstrual cycle, worse balance is generally reported when estrogen levels are high. Curiously, the direction of these results is counter to the observed sex differences in balance. While women generally show lower postural sway than men, the associations reported in literature have indicated that increases in estrogen are associated with increased postural sway; this seems counterintuitive given that men tend to have lower estrogen levels and higher sway. Although we found no clear relationship between estrogen levels and postural sway, on average we observed lower postural sway in participants with higher estrogen levels.

We might have observed significant differences over the course of the menstrual cycle if we had used different balance measures, but we elected to use a well-documented balance test with a large amount of normative data instead. Most previous studies investigating menstrual-cycle related fluctuations in balance control with objective measurement of balance have used custom instrumentation and reported measures in arbitrary units (Darlington et al., 2001; Fridén et al., 2003) or units that are specific to the balance testing apparatus (Maged et al., 2017; Sung & Kim, 2018). This makes it difficult to link experimental findings to any physical quantity to understand behavior. As such, we think that the easily replicable testing paradigm and interpretability of postural sway as a straightforward measure of postural control in the present study are important contributions.

Different timescales of fluctuations in estrogen levels and motor adaptation

While hormone levels vary cyclically over the course of the menstrual cycle, they also vary over lifetime via aging and with long-term exposure to exogenous hormones, for example via oral contraceptives. This study tested both those short-term fluctuations in the eumenorrheic cohort of participants and longer-term fluctuations between the eumenorrheic cohort and the cohort of participants using oral contraceptives. Although we did not find changes in postural control in either case, there is stronger evidence against changes due to short term fluctuations according to the day of the menstrual cycle than during long term fluctuations between eumenorrheic women and those using oral contraceptives.

In the context of connective tissue, several studies have not found changes in the structural properties of connective tissue over the course of the menstrual cycle (Burgess et al., 2009, 2010; Kubo et al., 2009). However, comparisons of men and women show differences in measures related to connective tissue properties (Beynnon et al., 2005; Shafiei et al., 2016), and some similar results are reported when comparing eumenorrheic women and those taking oral contraceptives (Bryant et al., 2008). These latter findings agree with changes that would be expected due to changes in connective tissue metabolism (Chidi-Ogbolu & Baar, 2019; Hansen,

2018; Leblanc et al., 2017) although much of the work in this area has not been performed in humans.

We did not find differences in postural sway related to changes in hormone levels due to oral contraceptive use or phases of the menstrual cycle. Other studies have also shown that, even though the physical properties of tissues change, other types of voluntary behavior like maximum voluntary force production does not change over the course of the menstrual cycle either (Bryant et al., 2008; Elliott et al., 2005). The central nervous system is able to compensate for numerous changes in the body over the course of development and aging to support our ability to successfully interact with the world over lifespan. Presumably changes in tissue properties, which may manifest themselves in differences in the effects of muscle activation or sensory inputs, are among the factors that the nervous system accommodates. One outstanding question is the timescale of this accommodation; while it may seem surprising that we could adapt to changes in the body so rapidly, motor adaptation paradigms routinely report adaptation on the timescale of hours (Maeda et al., 2020; Weiler et al., 2019) even in the context of supposedly “hard wired” responses like short-latency reflexes. Because we observed changes in plasma E_2 but no associated changes in balance, our results suggest that postural control could similarly quickly adapt to such systemic changes over the course of days during the menstrual cycle.

Concluding comments

While previous studies have investigated the effects of the menstrual cycle on balance, our study makes the following important contributions. First, we quantified balance using an easily understood measure (postural sway) which is reported in common physical units and can be compared to normative data from more than 16,000 people (Goble & Baweja, 2018b). Second, we recruited a large cohort of women (most previous studies have used under 20 participants total) whom we followed to obtain longitudinal data at four specific timepoints related to the menstrual cycle. Finally, and critically, we measured both plasma estradiol concentrations and postural sway in the same participants during the same visits, allowing us to directly investigate the potential relationship between hormone levels and balance, rather than using reported menstrual cycle phase as a proxy for hormone levels which vary widely among individuals.

Limitations

Balance or postural control is difficult to define, and postural sway is not a direct measure of balance. It is possible that our measure of sway did not capture some aspect of balance that is associated with changes in hormone levels. Additionally, in the context of sports injuries, the series of events that lead up to an injury (like a rapid change in direction) may not be closely linked with the factors measured via postural sway. Because of this, it is possible that there are balance- or injury-related measures that would be sensitive to changes in hormone level but which we did not capture using postural sway.

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Disclosures

The authors declare no conflicts of interest, financial or otherwise.

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