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Original article

The effect of physical activity across the menstrual cycle on reproductive function

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ABSTRACT

Purpose: To evaluate the association between physical activity (PA) across the menstrual cycle and reproductive function.
Methods: The BioCycle Study (2005–2007) followed 259 healthy premenopausal women not using hormonal contraceptives for up to two menstrual cycles ($N = 509$ cycles). Serum leptin, estradiol, progesterone, luteinizing hormone, follicle-stimulating hormone, and testosterone were measured five to eight times per cycle. Linear mixed models were used to estimate the effect of past-week PA (measured four times during each cycle) on hormone levels. Past-week PA was categorized into tertiles based on metabolic equivalent of task hours per week (cut-points were 15.3 and 35.7). Risk ratios for sporadic anovulation were estimated using generalized linear models. Analyses adjusted for habitual PA (assessed at baseline), body mass index, race, age, and perceived stress. Linear mixed models used inverse probability weights to control for concurrent reproductive hormones and caloric intake.
Results: High past-week PA was inversely associated with leptin (−6.6%; 95% confidence interval, −10.6 to −2.5) and luteal phase progesterone (−22.1%; −36.2 to −4.7) as compared with low past-week PA. High past-week PA was not significantly associated with sporadic anovulation (adjusted risk ratio, 1.5; 0.6 to 3.4).
Conclusions: High levels of PA were modestly associated with changes in select hormones but not sporadic anovulation among moderate to highly active premenopausal women.

Introduction

Physical activity (PA) is beneficial for women's health as it is associated with a decreased risk of cardiovascular disease, breast and colon cancers, type 2 diabetes, osteoporosis, and other adverse health outcomes [1]. The U.S. Department of Health and Human Services recommends that individuals engage in at least 150 minutes of moderate-intensity PA per week to gain these important health benefits [1]. As the majority (~70%) of reproductive-age women report meeting these guidelines [2], it is important to understand the effects of PA on reproductive hormones and ovulation, which can subsequently influence fertility outcomes.

There is evidence suggesting that high-intensity activity is associated with menstrual dysfunction and subfertility among high-performance female athletes [3]. Previous studies have found that high-intensity activity is associated with amenorrhea, oligomenorrhea, luteal phase deficiency, and anovulation, likely through disturbances of the hypothalamic-pituitary-adrenal axis [3,4]. It has been hypothesized that suppression of gonadotropin-releasing hormone resulting from exercise-associated hypothalamic dysfunction can delay menarche and disrupt menstrual cycle patterns by limiting the secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) [3,5].

Although much is known about PA and reproductive function among athletes, less is known about this association among more moderately active women. Several studies have examined the association between moderate levels of PA and menstrual cycle characteristics [6–8] or urinary and salivary hormone concentrations [9–12]. However, fewer studies have assessed the effect of PA on circulating hormone concentrations [13–15], and they were limited by assessing PA at only one time point and collecting blood at most two times across a menstrual cycle.

The primary objective of our study was to examine the association between PA and reproductive hormones, including estradiol,

Conflicts of interest: We declare we have no conflicts of interest.

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progesterone, LH, FSH, testosterone, and leptin, across the menstrual cycle. Our secondary objective was to examine the association between PA and the risk of sporadic anovulation. The effects of PA on reproductive function have important implications for fecundability and for modifying chronic disease risk across a woman's lifespan.

Methods

Study population

The BioCycle Study, conducted in 2005–2007, was a cohort study of 259 regularly menstruating, healthy premenopausal women from Western New York who were followed over one ($n = 9$) or two ($n = 250$) menstrual cycles. Women were ineligible for the study if they used oral contraceptives or medications for a chronic medical condition; were recently pregnant or breastfeeding; had been diagnosed with a menstrual or ovulatory disorder; planned to consume a restricted diet in the next 3 months or self-reported their body mass index (BMI) as less than 18 kg/m^2 or greater than 35 kg/m^2 at screening. Additional information about the study population is described elsewhere [16]. Among the 449 women screened for study participation, 319 met the eligibility criteria, 276 enrolled in the study, and 17 withdrew after enrollment. The University at Buffalo Health Sciences Institutional Review Board approved the study and served as the Institutional Review Board designated by the National Institutes of Health for this study under a reliance agreement. All participants provided written informed consent.

Measures

Reproductive hormones, anovulation, and menstrual cycle characteristics

Women provided morning fasting blood samples five to eight times per cycle. Fertility monitors (Clearblue Easy Fertility Monitor; Inverness Medical, Waltham, MA) were used to time mid-cycle visits, with the remaining visits scheduled according to an algorithm that considered each woman's typical cycle length [17]. For a standardized 28-day menstrual cycle, blood samples were collected during the following expected phases: menses (standardized day 2), follicular (standardized day 7), ovulatory (standardized days 12, 13, and 14), and luteal (standardized days 18, 22, and 27). Most women adhered to the study protocol with 94% providing at least seven blood samples per cycle. Samples ($N = 3903$) were processed according to standard protocols and frozen at −80°C within 90 minutes of phlebotomy [18]. They were then shipped on dry ice to analytical laboratories. Samples from each participant were batched together and measured consecutively to limit analytical variability.

Serum estradiol, progesterone, LH, and FSH levels were measured by solid-phase competitive chemiluminescent enzymatic immunoassays on the DPC Immulite 2000 analyzer (Siemens Medical Solutions Diagnostics, Deerfield, IL) at Kaleida Laboratories (Buffalo, NY). Serum total testosterone was measured by liquid chromatography/tandem mass spectrometry using the Shimadzu Prominence Liquid Chromatogram with an ABSceix 5500 tandem mass spectrometer at the Advanced Research and Diagnostics Laboratory (Minneapolis, MN). Increased sensitivity was achieved by using 100% acetonitrile mobile phase B as the solvent gradient elution and adding a low standard of 4 ng/dL. Serum leptin was measured by immunoassay using the Mercodia Leptin ELISA (Mercodia AB, Uppsala, Sweden) by the Advanced Research and Diagnostics Laboratory (discussed previously). The interassay coefficients of variation were as follows: <10% for estradiol; <14% for progesterone; <4% for LH and FSH; and <7% for testosterone. For leptin, select batches of measurements were recalibrated postassay by a calibration curve estimated from all the calibration data [19]. The interassay coefficient of variation for leptin was <10.2% after recalibration. Values falling below the limit of detection for each assay were rare (<3%) and were replaced with values equal to the limit of detection divided by the square root of two [20]. All hormones were logarithmically transformed for normality.

Anovulatory cycles ($n = 42$) were defined as cycles with a peak progesterone concentration ≤ 5 ng/mL and no observed serum LH peak among samples collected during the latter half of the cycle (i.e., days 22 and 27), which could indicate a missed luteal phase serum sample [21]. Menstrual cycle characteristics (menstrual cycle length, follicular and luteal phase length, menses length, and total blood loss during menses) were determined from fertility monitor data, serum hormone levels, daily diaries, and pictograms for documenting total blood loss [21,22].

Physical activity

There were three measures of self-reported PA: habitual PA (measured at baseline using the long-form International Physical Activity Questionnaire, IPAQ [23,24]); past-week PA (measured on days 2, 7, 14, and 22 using the short-form IPAQ); and daily vigorous PA (measured using a daily diary). Both IPAQs assessed the duration and frequency of walking, moderate activity, and vigorous activity lasting for at least 10 minutes during the previous week, with the long-form IPAQ including additional questions about specific types of activity. Total metabolic equivalent of task-hours per week (MET-h/wk) were calculated by summing the individual MET-h/wk for each activity according to published guidelines [24]. Past-week PA was further classified using the MET-h/wk spent in vigorous activity only and termed "vigorous past-week PA." For daily vigorous PA, participants were instructed to record the amount of time spent each day engaged in vigorous activity, defined as "activities that take hard physical effort and make you breathe much harder than normal."

For the measure of habitual PA, women were categorized into tertiles based on MET-h/wk reported. For average past-week PA, the MET-h/wk from the short-form IPAQs were averaged across each cycle and across the entire study period for each individual and then categorized into tertiles, respectively. For the time-varying analyses, past-week PA was categorized into tertiles based on the distribution of MET-h/wk reported at each assessment, thus a woman could be categorized as having high past-week PA at one assessment and low past-week PA at another. In addition, tertile cut-points varied by assessment day as the distribution of MET-h/wk varied. Daily vigorous activity for the day before serum collection was dichotomized as any versus none.

Covariates

Self-administered questionnaires were used to assess demographics, smoking behavior, and perceived stress (measured by the 14-item Cohen Perceived Stress Scale) [25] at study enrollment. BMI was calculated using weight and height as measured by trained personnel at the baseline visit. Total caloric intake was assessed by four 24-hour dietary recalls measured during each cycle.

Statistical analysis

Participant characteristics were compared by tertile of average past-week PA across the study period with Fisher exact and analysis of variance tests used to evaluate differences. For repeated measures within individual women (i.e., from multiple cycles and days), unadjusted linear mixed models were used to calculate means and assess differences across PA tertiles for continuous variables and unadjusted generalized linear models were used to assess