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Sexual activity, endogenous reproductive hormones and ovulation in premenopausal women ☆,☆☆

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ABSTRACT

We investigated whether sexual activity was associated with reproductive function in the BioCycle Study, a prospective cohort study that followed 259 regularly menstruating women aged 18 to 44 years for one (n = 9) or two (n = 250) menstrual cycles in 2005–2007. Women were not attempting pregnancy nor using hormonal contraceptives. History of ever having been sexually active was assessed at baseline and frequency of sexual activity, defined as vaginal–penile intercourse, was self-reported daily throughout the study. Serum concentrations of estradiol, luteinizing hormone (LH), follicle-stimulating hormone (FSH), progesterone, and testosterone were measured up to 8 times/cycle. Sporadic anovulation was identified using peak progesterone concentration. Linear mixed models were used to estimate associations between sexual activity and reproductive hormone concentrations and generalized linear models were used to estimate associations with sporadic anovulation. Models were adjusted for age, race, body mass index, perceived stress, and alcohol consumption and accounted for repeated measures within women. Elevated concentrations of estrogen (+14.6%, $P < .01$), luteal progesterone (+41.0%, $P < .01$) and mid-cycle LH (+23.4%, $P < .01$), but not FSH ($P = .33$) or testosterone ($P = .37$), were observed in sexually active women compared with sexually inactive women (no prior and no study-period sexual activity); sexually active women had lower odds of sporadic anovulation (adjusted odds ratio = 0.34, 95% confidence interval: 0.16–0.73). Among sexually active women, frequency of sexual activity was not associated with hormones or sporadic anovulation (all $P > .23$). Findings from our study suggest that ever having been sexually active is associated with improved reproductive function, even after controlling for factors such as age.
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Introduction

Ovulation in women is thought to occur spontaneously during each menstrual cycle, regardless of sexual behavior, as a result of positive and negative feedback mechanisms of the hypothalamic–pituitary–ovarian axis (Adams and Ratto, 2013). However, given the potential evolutionary benefits of sexual activity influencing ovulatory function and consequent pregnancy success (Wilcox et al., 2004) and the evidence that sexual activity induces ovulation in other species (Bakker and Baum, 2000; Jöchle, 1975; Pfaus et al., 2003; Wu et al., 1977), it remains to be established whether or not humans have similar biological mechanisms in place to induce or augment ovulatory function (Stanislaw and Rice, 1987; Wilcox et al., 2004).

Female- versus male-initiated sexual activity has been shown to be greater around the time of ovulation (Adams et al., 1978; Gangestad et al., 2002; Harvey, 1987; Wallen, 2001) and numerous studies have found that sexual activity among women in general peaks during the time of ovulation (Bullivant et al., 2004; Caruso et al., 2014; Pagidas et al., 2010; Van Goozen et al., 1997; Wilcox et al., 2004) as does the desirability of a male partner (Larson et al., 2013). Together these studies suggest that peri-ovulatory hormonal patterns may cause an increase in female libido, which together with their partner's desire and the couple's intentions regarding pregnancy, can affect sexual behavior (Wallen, 2001).

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Further characterization of the relationship between sexual activity and reproductive function has the potential to improve our understanding of couples' fecundity (Buck Louis, 2011). A recent review concluded that although the relationship between sexual activity and menstrual cycle function has been studied, several conflicting results and methodological differences make it difficult to draw definitive conclusions (Brown et al., 2011). Previous studies have evaluated sexual activity patterns across the menstrual cycle, but have been limited in their examination of sexual activity and ovulatory function, have not included a comparison of reproductive function between sexually active women and women reporting no history of sexual activity, nor have evaluated the effect of reproductive function during one cycle on sexual activity in a subsequent cycle.

Therefore, we investigated the association between sexual activity and reproduction function, examining both the effect of sexual intercourse on reproductive function and the effect of reproductive function on sexual intercourse using longitudinally collected data. Our hypotheses were that sexually active women would have higher reproductive hormone levels and be less likely to experience anovulatory cycles compared with sexually inactive women and that reproductive hormones would be associated with sexual activity patterns. We investigated these hypotheses in a cohort of healthy premenopausal women, both with or without a history of sexual activity, who were not attempting pregnancy nor using hormonal contraceptives.

Materials and methods

Study population

The BioCycle Study was a prospective cohort study that included 259 healthy, regularly menstruating women aged 18 to 44 years from western New York State during 2005–2007 and followed them for up to two menstrual cycles. Details of the study population, materials and methods have been previously described (Wactawski-Wende et al., 2009). Briefly, exclusion criteria included use of oral contraceptives within the past 3 months; a history of pregnancy, breastfeeding, or attempting a pregnancy within the past 6 months; and any recent history of infection or diagnosis of a chronic medical condition, including menstrual and ovulatory disorders, or psychiatric condition, including premenstrual dysphoric disorder. In addition, women with a self-reported body mass index (BMI) of <18 or >35 kg/m^2 at screening were excluded. The University at Buffalo Health Sciences Institutional Review Board (IRB) approved the study and served as the IRB designated by the National Institutes of Health for this study under a reliance agreement. All participants provided written informed consent. The main findings of the study concerning reproductive hormones and oxidative stress have been previously published (Schisterman et al., 2010).

Fasting blood samples were scheduled to be collected in the morning (between 7 and 8:30 am) at up to 8 visits per cycle planned to occur during menses; the mid-follicular phase; three days around the time of the luteinizing hormone (LH) surge; and the early, mid, and late luteal phases. The timing of visits was facilitated by the use of home fertility monitors (Clearblue Easy Fertility Monitor; Inverness Medical, Waltham, Massachusetts) (Howards et al., 2009). Nearly all women (94%) provided 7 or 8 blood specimens per cycle and 100% provided at least 5 specimens per cycle.

Blood collection and handling protocols were designed to minimize variability (Wactawski-Wende et al., 2009). All samples were processed and frozen at −80 °C within 90 min of phlebotomy and analytes were measured in participant-specific batches within a single run to limit analytical variability. Estradiol, LH, follicle-stimulating hormone (FSH), and progesterone concentrations were measured in serum samples using solid-phase competitive chemiluminescent enzymatic immunoassays (DPC Immulite 2000 analyzer, Siemens Medical Solutions Diagnostics, Deerfield, IL) at the Kaleida Health Center for Laboratory Medicine (Buffalo, NY). Serum testosterone was measured by liquid chromatography/tandem mass spectrometry (Shimadzu Prominence Liquid Chromatogram with an ABSceix 5500 tandem mass spectrometer) by the Advanced Research and Diagnostic 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. The interassay maximum coefficients of variation reported by the laboratory were $\leq$10% for estradiol; $\leq$5% for LH and FSH; $\leq$14% for progesterone; and $\leq$7% for testosterone. All hormone measurements were log-transformed for normality before statistical analysis and then transformed by exponentiation for table display. In addition, LH and progesterone measurements were restricted in the analysis to mid-cycle (three days around the LH surge) and luteal phase (early, mid and late), respectively, as these are the phases with the greatest biological variance for these hormones. For certain analyses, progesterone measurements from mid-cycle visits were also analyzed for comparison.

Sporadic anovulatory cycles were defined as cycles with peak serum progesterone concentrations $\leq$5 ng/mL and no observed serum LH peak during the mid or late luteal phase visits (Gaskins et al., 2009). These cycles were considered to reflect sporadic rather than chronic anovulation, as study participants were healthy women without reported gynecological or menstrual disorders.

Sexual activity and covariate assessment

Participant characteristics, such as race, age, and smoking status, were assessed during a baseline visit via questionnaire. Trained study staff measured height and weight, from which BMI was calculated. Perceived stress level was measured using the 14-item Cohen Perceived Stress Scale (PSS) (Cohen et al., 1983). In addition, prior sexual history was ascertained by the question: "Have you ever been sexually active? (Y/N)". Among sexually active women, contraceptive use history was obtained.

Sexual activity during the study period was assessed prospectively using a daily diary where participants reported whether they had engaged in sexual intercourse, defined as vaginal–penile intercourse, that day (Y/N), with instructions that participants should consider that each day ends at midnight. Alcohol intake was also assessed via the daily diary and was averaged over the study period and subsequently categorized as: low ($\leq$0.5 drinks/day), moderate (0.5 to 1 drinks/day), or high ($\geq$1 drinks/day). The daily diary also captured information on medication use, hours of sleep, and minutes of vigorous physical activity.

Statistical analysis

Baseline characteristics, sexual history, and contraceptive use history were compared among participants grouped into four sexual activity categories: (1) no prior and no current sexual activity during the study period (henceforth labeled "sexually inactive"), (2) history of sexual activity but not during the study-period ("not sexually active during study"), (3) weekly or less during the study-period ("weekly or less"), and (4) greater than weekly during the study-period ("greater than weekly"). Fisher's exact tests were used to test for differences among sexual activity categories for categorical variables and analysis of variance was used for continuous variables. In addition, pair-wise comparisons were performed between sexual activity categories on mean reproductive hormone concentrations, with the Tukey method used to account for multiple comparisons.

Variation in reported daily sexual activity across the menstrual cycle among women sexually active during the study was assessed using linear mixed models to account for repeated measures within women. Days were aligned in relation to the day of ovulation, which was estimated based on dates and levels of LH peak from the fertility monitor compared with the observed LH maximum value in serum and the first day of progesterone rise (Mumford et al., 2012). If the cycle was classified as anovulatory, cycle day 14 was assigned as the estimated day of ovulation for comparison purposes. Pair-wise comparisons were made