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ORIGINAL ARTICLE

Elevated Psychological Stress Predicts Reduced Estradiol Concentrations in Young Women

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Abstract There has long been much interest in whether psychological stress may have inhibitory effects on ovarian hormone production and associated fecundity in women, but previous research has been inconclusive. The present study assessed whether hormone concentrations were lower on days with higher self-perceived stress than on days with lower stress within the same menstrual cycles. Results demonstrated a clear negative relationship between current day stress ratings and salivary estradiol concentrations (but not concentrations of testosterone or progesterone). This effect survived controls for potential confounding variables related to food intake, cold symptoms, exercise duration, and hours of sleep. Likewise, the effect was still present when controlling for day of the menstrual cycle, and elevated stress was associated with suppressed estradiol across broad regions of the cycle. These findings provide direct evidence for an inhibitory effect of psychological stress on ovarian hormone production, and thus recommend future research designed to further elucidate the relevant physiological mechanisms.

Keywords Stress · Estradiol · Fecundity · Menstrual Cycle · Reproductive suppression

It has long been theorized that psychosocial stress may inhibit reproductive function in women (e.g., Wasser and Isenberg 1986). Although it is now well-established that energetic stress can suppress ovarian function in both human and nonhuman species (for reviews, see Ellison 2001; Loucks and Redman 2004; Wade and Jones 2004), evidence for additional effects of psychosocial stress has been less definitive.

In nonhuman mammals, experimentally induced stressors such as social isolation, blindfolding, or presentation of predator sounds have been shown to induce increased cortisol and decreased gonadotropin production (Xiao et al. 2002; Wagenmaker et al. 2009;

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O'Connor et al. 2011), reduced luteal phase progesterone (Xiao et al. 2002; O'Connor et al. 2011), and reductions in estrogen-dependent sexual swellings (O'Connor et al. 2011) or sexual behavior (Wagenmaker et al. 2009). Such changes have been demonstrated despite the absence of changes in diet (O'Connor et al. 2011) or body weight (Xiao et al. 2002), suggesting that ovarian suppression was not an artifact of reduced food intake associated with the stressors. One causal model suggested by these results is that psychological stress triggers cortisol responses that in turn cause ovarian suppression. Other research, however, has shown that psychosocial stress can inhibit gonadotropin production even among adrenalectomized animals or those administered glucocorticoid receptor antagonists (see Wagenmaker et al. 2009; for reviews, see Ferin 1999; Tilbrook et al. 2002), thus suggesting that cortisol increases are not always necessary for stress-induced reproductive suppression.

In humans, a small number of prospective studies have provided evidence for lower self-reported anxiety and distress in successful conception vs. nonconception cycles within the same women (e.g., Sanders and Bruce 1997; Hjollund et al. 1999), though other research has failed to find an effect of perceived stress on time to pregnancy (Lynch et al. 2012). Some evidence implicates physiological correlates of psychological stress in reproductive suppression: higher salivary alpha-amylase concentrations predicted lower fecundability odds ratios in a sample of women trying to conceive (Louis et al. 2011), higher adrenaline and noradrenaline concentrations measured during oocyte retrieval or embryo transfer predicted lower success rates for in-vitro fertilization (IVF) treatments (Smeenk et al. 2005), and elevated cortisol was associated with early pregnancy loss in a sample of Guatemalan women (Nepomnaschy et al. 2006). Anxiety has often been proposed to predict lower IVF success rates (see review in Smeenk et al. 2005), though direction of causality is sometimes ambiguous in such research, and other studies have reported null associations with psychological stress (e.g., Anderheim et al. 2005). Finally, some research has reported that infertility patients randomized to psychological treatments designed to reduce stress conceived faster than did patients randomized to control conditions (e.g., Domar et al. 2000; for a review, see de Liz and Strauss 2005).

Given evidence that salivary estradiol concentrations positively predict conception probabilities among women attempting to conceive (Lipson and Ellison 1996; Venners et al. 2006), effects of stress on reproductive functioning could be assessed via tests of associations between perceived stress and production of salivary estradiol. Ellison et al. (2007) reported that mean salivary estradiol and progesterone concentrations did not differ within-women in cycles measured before and after an exam stressor, nor between women who differed in self-reported levels of stress or trait anxiety. Although that research suggests that moderate levels of stress or anxiety may be insufficient to suppress ovarian hormone production in women, the investigators tested only mean hormone concentrations within specific cycle regions and did not test day-to-day associations between perceived stress and hormone production within the same women. The design of the current study allowed examination of possible relationships between stress and ovarian hormones at this more fine-grained level of temporal resolution.

In the present research, young women provided daily saliva samples from which were assayed concentrations of estradiol, progesterone, and testosterone, and also completed a daily survey in which they indicated self-perceived levels of stress. Based on the evidence reviewed above for conception probabilities being positively

related to estradiol concentrations but negatively related to psychological stress, we hypothesized a negative relationship between self-perceived stress and concentrations of salivary estradiol. Based on the nonhuman studies reviewed above, we tested the additional hypothesis that higher stress would predict lower progesterone concentrations. Relationships between testosterone and stress were considered exploratory.

The daily survey contained a number of other measures that might act as lurking variables that could produce associations between stress and ovarian hormone concentrations even if there were no causal effects of perceived stress. For instance, if poor sleep or cold symptoms caused women to feel more stressed and also led to reductions in ovarian hormone production, then a stress-hormone relationship could arise even absent any causal effects of stress on hormones. Given known effects of energetic stressors on ovarian hormone production (see Loucks and Redman 2004; Ellison et al. 2007), we tested relationships between stress and hormones when controlling for items in the daily survey that were related to energetics, including food intake, exercise intensity, hours of sleep, and cold symptoms.[1]

Methods

Participants

Women participants were part of a broader study that was primarily designed to assess relationships between ovarian hormones and sexual psychology and behavior (see Roney and Simmons 2013). Pregnancy, lactation, or any use of hormonal contraceptives or steroid medications within the last 6 months were exclusion criteria, as were self-reported menstrual cycles longer than 40 days. Fifty-two women participated for 1–2 menstrual cycles, with a total of 37 women having participated in both cycles. Because the perceived stress variables appeared in the daily survey for the second cycle only, data analyses in the present report were restricted to the second cycle. Hormone assays were not performed for one woman in this cycle with many missing saliva samples, such that the final sample size was n=36 (mean age =18.7 years). Further details regarding this sample appear in Roney and Simmons (2013). Participants provided written, informed consent for participation; the research was approved by the UCSB Institutional Review Board; and all procedures were in accordance with the Code of Ethical Principles for Medical Research Involving Human Subjects of the World Medical Association (Declaration of Helsinki).

Materials

Participants completed a daily survey via a secure website each morning beginning on the day of menses onset and continuing until the end of their cycle. This survey contained a

[1] Importantly, these controls were not intended to test whether perceived stress affects ovarian hormones independent of the catabolic (and thus energetic) effects of cortisol in response to stress. If psychological stress triggers cortisol increases that in turn reduce ovarian hormone production, stress would still be the cause of ovarian suppression via the cortisol increases. By contrast, if illness caused both higher stress and reduced ovarian production, stress would not necessarily be causal. The controls were intended to provide evidence against scenarios of the latter kind.

number of items related to sexual desire and behavior that are not analyzed in the present report. Two items assessed perceived stress. The first read: "Overall, how stressful was your day yesterday?" with the response scale running from 1 (much less than usual) to 5 (much more than usual). The second item read: "Remembering back to yesterday, did you feel like you were under more stress than you could deal with?" with the scale running from 1 (not at all) to 5 (most of the day). A large number of previous studies have employed single-item measures of perceived stress similar to the first item, and such measures have been validated via correlations with composite ratings of lists of stressors (Brantley et al. 1987), fluctuations in physical symptoms (e.g., Levy et al. 1997), and physiological measures such as blood pressure and heart rate (Pollard et al. 2007). In order to be comparable to past studies that have used single-item measures of stress, then, the first item was chosen as a continuous measure of perceived stress, though reported results were very similar if a composite measure comprised of the mean of the two stress items (r=0.73) was used instead. Participants were also given the option of providing a free-response listing of any particularly stressful events that occurred on the response day; only 50 such events across all participants were listed on days for which hormone values were available, which limited power for analyzing responses to specific types of stressors. As such, the free response listings were not analyzed in the present report (the most commonly listed stressor was exam stress, comprising 30 of the 50 reports).

The daily survey also contained the items that were tested as possible confounding variables for the hypothesized relationship between stress and ovarian hormones. Cold symptoms were measured as a binary variable (yes/no regarding whether they were experienced on the response day), sleep duration was simply reported in hours, and exercise intensity was a categorical variable defined by min of exercise (0, 0–15, 15–30, 30–60, or greater than 60 min). Food intake was measured via a global item, "How much did you eat yesterday?" (1–5 scale running from much less to much more than usual), as well as by ratings of meal size (for each meal consumed, the participants rated from 1–5 the size of the meal running from much smaller to much larger than usual; 0 was assigned if the specific meal was skipped, and values were then averaged across the three meals); a mean of the global rating and average meal size rating (r=0.57) served as the composite food intake variable. Because survey items referred to "yesterday," responses were aligned with hormone concentrations from the previous day.

Saliva Collection Procedure and Hormone Assays

Women collected saliva samples each morning via passive drool into polypropylene vials. Samples were initially stored in home freezers and then delivered weekly to our research lab, after which they were replaced with new vials. The samples were then stored at −80 C until being shipped for assay. Out of 928 eligible cycle days across the 36 women, samples were obtained for 849 days for a compliance rate of 91.5 %. Prior to shipping, we estimated the day of ovulation as 15 days prior to the end of each cycle and then sent for assay each of the available saliva samples in a nine day window centered on this day, as well as samples from alternating days outside of this window. In total, 562 samples were shipped for assay, corresponding to 1686 requested assays across the three hormones.

Saliva samples were shipped on dry ice to the Endocrine Core Laboratory at the California Regional Primate Research Center, Davis, CA, where they were assayed for

concentrations of estradiol, testosterone, and progesterone. Full details of the assay procedures can be found in Roney and Simmons (2013); intra- and inter-assay CVs were below 10 % for each of the hormones. Out of the 1686 requested assays, insufficient saliva for all three analytes led to a total of 1645 assay values for use in the present study. Hormone concentrations more than 3 SD from their respective means (n=24 across the three hormones) were removed to avoid undue influence of outliers (see Roney and Simmons 2013), though no statistical conclusions were altered by doing so.

Data Analyses

Linear mixed regression models in SPSS v20 were used to test whether day to day fluctuations in ovarian hormone concentrations were predicted by fluctuations in perceived stress or the potential confounding variables related to energetics. These models estimate the within-cycle relationships between independent and dependent variables averaged across all women in the sample. A subject-level error term for the intercept was included in all models. Continuous variables were first standardized relative to their respective grand means in order to make the regression coefficients similar to standardized beta coefficients. Predictor variables were then group-mean centered within-cycles before entry at Level-1. A first-order autoregressive error structure was specified at Level-1 in order to account for autocorrelation in the hormone concentrations.

We first tested the zero-order associations of perceived stress with each of the measured hormone variables in separate regression models. Each of the potential confounding variables (see Materials) were tested for zero-order relationships with the hormone dependent variables, and those with $p<0.10$ were then added to the regression models containing the daily stress variable. To account for possible time delays in the effects of the predictor variables, we tested for associations with hormone concentrations when predictors referred to the same day as the measured hormone values, one day earlier, and two days earlier.

Finally, in order to control for region of the cycle when predicting hormone concentrations, we estimated day of ovulation among those cycles judged ovulatory. Following Ellison et al. (1987), we designated as ovulatory cycles with maximum progesterone values of at least 300 pmol/L (24 of 36 cycles met this criterion). For these cycles, we followed Lipson and Ellison (1996) in assigning the day of ovulation as the second of the two consecutive days between which the largest drop in estradiol occurred after the day of peak estradiol (if the day following the estradiol peak had missing hormone data, it was designated the day of ovulation). Cycle days were then divided into bins relative to the estimated day of ovulation as day zero (bins were defined as follows: < day −9, −9 to −7, −6 to −4, −3 to −1, 0 to +1, +2 to +4, +5 to +7, +8 to +10, and >+10), and these bins were then added to regression models as a categorical variable (with one bin omitted) in order to control for region of the cycle in specific data analyses. For construction of one particular graph (Fig. 2), we also divided the cycle into broader regions comprised of the fertile window (i.e. days of the cycle when conception is possible, running from −5 to 0; see Wilcox et al. 1998), follicular phase days prior to the fertile window, and luteal phase days (i.e. > day 0). Analyses that tested effects of cycle region were performed on the subset of women with ovulatory cycles (n=24), whereas the other analyses included all women (n=36).

Results

Current day perceived stress negatively predicted within-cycle fluctuations in estradiol concentrations, γ=−0.11, *df*=426.27, *p*=0.009, CI: −0.20 to −0.03, whereas stress ratings from one and two days earlier were unrelated to estradiol (*p*s>0.20). Figure 1 provides a visual depiction of the within-cycle, zero-order association between current day stress and estradiol concentrations; it can be seen that there was no tendency for estradiol to drop when moving from below average to average levels of stress, whereas days on which stress was rated higher than usual were associated with clear reductions in estradiol relative to other days in the same cycles. This pattern suggests that a dichotomous high/low stress variable may better capture the relationship between stress and estradiol, and indeed a binary variable coded 1 for scale scores of 4 or 5 but coded 0 otherwise was a stronger predictor of estradiol concentrations than was the original current day stress variable: γ=−0.28, *df*=431.10, *p*=0.003, CI: −0.46 to −0.10.

Contrary to the effects for estradiol, there were no significant within-cycle relationships between stress ratings and either progesterone or testosterone concentrations at any time lag (statistics for effects of current day stress: γ=−0.06, *df*=380.66, *p*=0.15, CI: −.14 to .02 for progesterone; and γ=−0.02, *df*=439.59, *p*=0.58, CI: −.10 to .05 for testosterone). Null effects of current day stress on progesterone persisted when analyses were restricted to the estimated luteal phase (γ=−0.14, *df*=129.09, *p*=0.16, CI: −.35 to 0.06), although the larger effect size suggests that a luteal effect might be detected with greater power. Given the null effects for progesterone and testosterone, tests of relationships between the potential confounding variables and hormone values were restricted to estradiol concentrations.

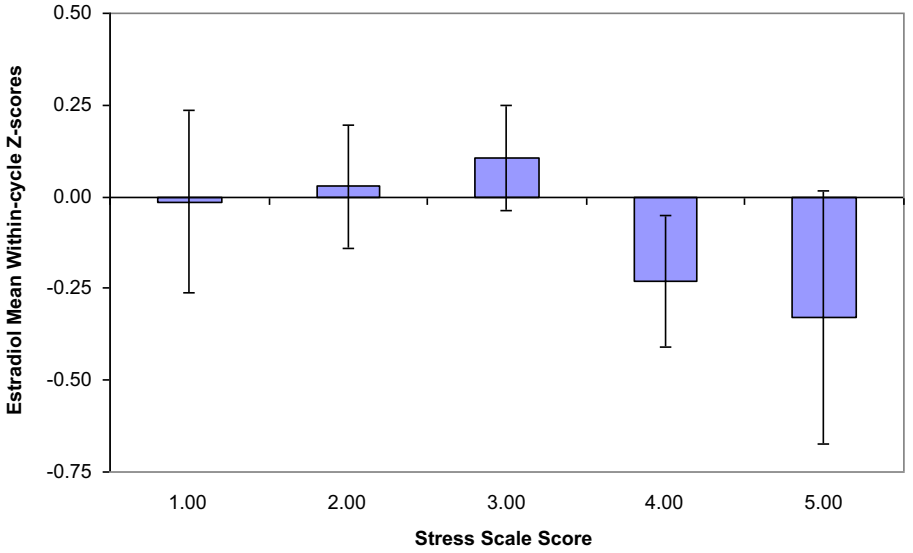

Fig. 1 Mean estradiol concentrations plotted against stress scale ratings (1 indicated that the day was much less stressful than usual, 3 indicated usual levels of stress, and 5 indicated that the day was much more stressful than usual). Estradiol values were standardized within-cycles such that the zero point on the y-axis indicates mean estradiol within a given cycle. Error bars are 95 % confidence intervals.

Among the four potential confounding variables related to energetics, two were at least marginally associated with salivary estradiol concentrations: hours of sleep the previous night was a positive predictor of within-cycle fluctuations in estradiol (γ=0.10, *df*=395.90, p=0.011, CI: 0.02 to 0.18), while the presence of current day cold symptoms was a negative predictor (γ=−0.21, *df*=350.28, p=0.055, CI: −0.43 to 0.004). Table 1 demonstrates that the negative effect of current day stress (using the original continuous variable) on estradiol concentrations was still present when the sleep and illness variables were entered into the same model.

Although the relationship between stress and estradiol was hypothesized based on the idea that stress inhibits estradiol rather than vice-versa, the correlational nature of the data leaves direction of causality ambiguous. If higher estradiol leads to perception of events as less stressful, then one would expect higher estradiol regions of the cycle to be associated with lower stress ratings, and for the relationship between stress and estradiol to be at least partially accounted for by day of cycle. The within-cycle effect of cycle day bins on estradiol concentrations was large (F (8, 228.29) =14.19, p=0.0001 for the overall effect of the categorical variable), but there was no comparable effect of cycle day bins on stress ratings (F (8, 206.98) =1.31, p=0.24). Estradiol was by far the highest in the bin spanning days −3 to −1, as expected, but stress ratings were actually nonsignificantly *higher* in this bin compared to all others, γ=0.14, *df*=189.89, p=0.33, CI: −0.14 to 0.43, which works against the hypothesis of a negative relationship between stress and estradiol. Finally, when cycle day bins were added to the model depicted in Table 1, the negative effect of perceived stress on estradiol concentrations was still present, γ=−0.11, *df*=262.48, p=0.014, CI: −0.21 to −0.02.

Figure 2 provides one means of visualizing the within-woman relationship between stress and estradiol within specific cycle regions. For each woman in each of the identified cycle bins, we computed mean estradiol values on low (scale scores 1–3) and high (scale scores 4–5) stress days and then subtracted the high mean from the low mean; the bars in Fig 2 thus depict the mean differences in estradiol on low vs. high stress days when each woman contributes at most one difference score in each cycle bin. It can be seen that estradiol was higher on low stress days in all three broad regions of the cycle, but that the effect was especially pronounced inside the estimated fertile window: on average, when a woman reported a high stress day in the fertile window,

Table 1 Mixed regression model testing within-cycle predictors of estradiol concentrations[1]

Predictor	Coefficient (γ)	Standard error	df[4]	p-value	95 % Confidence interval
Stress rating[2]	-0.11	0.045	403.57	0.019	-0.19 to -0.02
Hours of sleep[2]	0.072	0.040	342.44	0.076	-0.01 to 0.14
Cold symptoms[3]	-0.23	0.11	333.90	0.041	-0.46 to -0.01

[1] Estradiol concentrations were standardized relative to the grand mean as the dependent variable.

[2] Stress and hours of sleep were first standardized relative to their respective grand means and then group-mean centered within-cycles.

[3] Cold symptoms was a dummy coded variable.

[4] *DF* reflect the Satterthwaite correction as generated by the SPSS program.

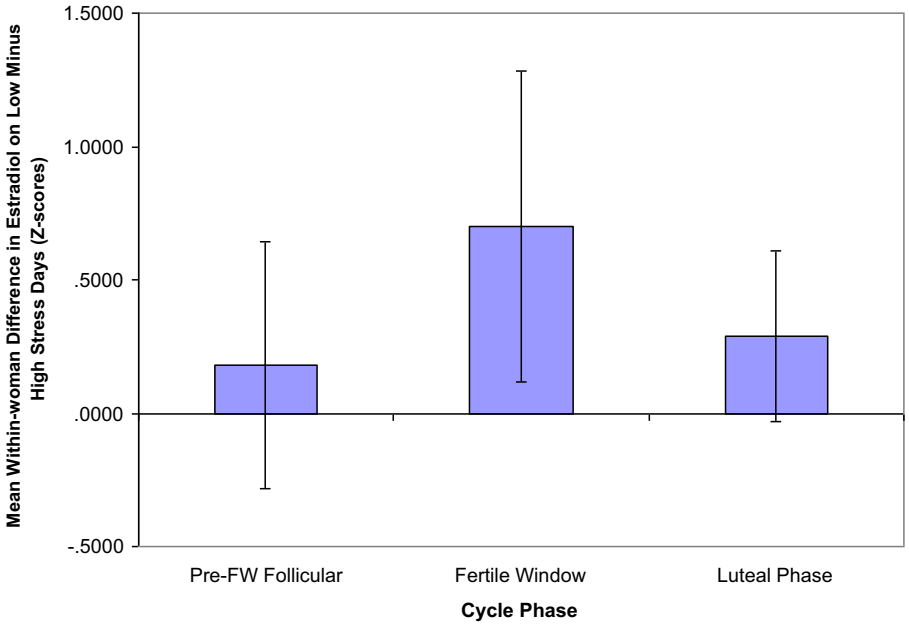

Fig. 2 Mean differences between average estradiol concentrations on low stress days (stress scale ratings 1–3) and high stress days (stress scale ratings 4–5) computed within-women within the indicated cycle regions (see text for further explanation). Estradiol values were standardized within-cycles before computing difference scores such that scores are in units of cycle-specific standard deviations. Error bars are 95 % confidence intervals

her estradiol concentrations were 0.70 standard deviations lower than on low stress days within the same fertile window. This pattern suggests that stress may blunt the size of the pre-ovulatory estrogen surge.

Discussion

The present study is to our knowledge the first to have tested within-cycle relationships between psychological stress and ovarian hormone production. The results demonstrated that days with higher stress ratings were characterized by lower salivary estradiol concentrations compared to days with lower stress ratings within the same cycles. There was no evidence that this effect was an artifact of energetic factors related to illness, sleep duration, food intake, or exercise duration. Because some data suggest that estradiol may reduce physiological responses to stressors (e.g., Komesaroff et al. 1999), our correlational finding might be explained by an influence of estradiol on stress perception rather than vice-versa. However, there was no evidence that the correlation demonstrated here was an artifact of a tendency to perceive events as less stressful when estradiol concentrations were elevated, as high estradiol regions of the cycle were not associated with lower stress ratings, and the negative association between stress and estradiol persisted when region of the cycle was held constant. As such, the overall pattern of results is consistent with perceived stress having caused the reduction in estradiol concentrations.

The predicted effect of psychological stress on progesterone concentrations was not confirmed. Stressors of longer duration have been associated with progesterone reductions in nonhuman species (e.g., Xiao et al. 2002; O'Connor et al. 2011). Because progesterone production tends to be consistently low across the follicular phase, an effect of stress on progesterone may be more likely specifically during the luteal phase, and we did in fact observe a larger effect size for the non-significant relationship between stress and progesterone when analyses were restricted to days within the estimated luteal phase (see Results). This pattern suggests the potential value of additional research on the relationship between stress and luteal progesterone, ideally with larger sample sizes.

The present findings in conjunction with previous studies that have provided evidence for cycles with higher perceived stress having lower odds of conception (e.g., Sanders and Bruce 1997; Hjollund et al. 1999) suggest a model of reproductive suppression in which psychological stress causes lower estradiol production, which in turn predicts lower fecundity (Lipson and Ellison 1996; Venners et al. 2006). Elevated stress ratings in the present sample were generally transient and as such may not have appreciably affected fecundity in the sampled cycles, but high stress scale scores were associated with temporary reductions of estradiol of about 0.30 standard deviations overall (see Fig. 1) and 0.70 standard deviations specifically within the fertile window (see Fig. 2), suggesting that more sustained stress of this intensity might lead to substantial reductions in the overall production of estradiol.

Perceived stress could affect estradiol production through various mediating pathways. Cortisol has been shown to have inhibitory effects on the hypothalamic-pituitary-gonadal (HPG) axis (for reviews, see Ferin 1999; Tilbrook et al. 2002) and is known to be released in response to psychological stress (see Dickerson and Kemeny 2004), such that effects of perceived stress on estradiol may have been mediated by cortisol. Research in some nonhuman species has demonstrated suppressive effects of psychosocial stress on gonadotropins even among adrenalectomized animals or those administered glucocorticoid receptor antagonists (see Wagenmaker et al. 2009; for reviews, see Ferin 1999; Tilbrook et al. 2002), however, which implicates other mediating signals. A range of other signals have in fact been associated with HPG inhibition, including corticotrophin releasing hormone (CRH), arginine vasopressin (AVP), endogenous opioid peptides, and catecholamines associated with sympathetic activation (Ferin 1999; Tilbrook et al. 2002). That such signals can inhibit HPG activity independent of cortisol increases is interesting because it suggests that central mechanisms involved in the perception of stress might reduce hormone production even absent catabolic states associated with glucocorticoid production. Additional research is necessary to test which signals may mediate relationships between perceived stress and estradiol production specifically in humans.

A limitation of our study concerns the self-report nature of our stress variable and the potential confounding variables related to energetics. Although single-item measures of self-perceived stress have been previously validated via correlations with both longer self-report scales (e.g., Brantley et al. 1987) and physiological measures (e.g., Pollard et al. 2007), the collection of putative biomarkers of psychological stress (such as salivary cortisol or alpha-amylase) would be preferable as additional sources of validation. Likewise, variables like food intake, sleep duration, and presence of cold symptoms could all be measured more precisely than by self-report, although sleep

and cold symptoms were apparently measured well enough to significantly predict within-cycle fluctuations in estradiol concentrations, but nonetheless failed to account for the relationship between perceived stress and estradiol (see Table 1). Countervailing strengths of our study include its frequent sampling of both ovarian hormones and self-perceived stress, which allowed novel tests of the day-to-day associations between these variables. The consistent negative, within-cycle relationship between stress and estradiol revealed by those tests suggests the importance of additional research on this topic.

In conclusion, the present study provides original evidence that self-perceived stress is associated with reduced estradiol production in young women. This effect could be part of an adaptive mechanism designed to temporarily inhibit reproduction under aversive circumstances (see Wasser and Isenberg 1986), although additional evidence is necessary to test this possibility. Future research is also needed to determine the physiological links between perceived stress and ovarian hormone production, and to link the observed reductions in estradiol concentrations to more direct measures of fecundity.

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Ethics Statement Participants provided written, informed consent for participation; the research was approved by the UCSB Institutional Review Board; and all procedures were in accordance with the Code of Ethical Principles for Medical Research Involving Human Subjects of the World Medical Association (Declaration of Helsinki). The authors declare that they have no conflict of interest.

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