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(Article begins on next page)

TITLE: Weight change and ovarian steroid profiles in young women

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CAPSULE

Young women who gained weight during a menstrual cycle had more distinct follicular and luteal estradiol peaks than those who lost weight, and peak progesterone occurred about two days earlier.

ABSTRACT

Objective: To investigate possible short-term effects of voluntary weight loss on ovarian steroid profiles in young women, in light of better established long-term effects in older women.

Design: We tested for an association of voluntary weight change over the course of a menstrual cycle with salivary estradiol and progesterone profiles in the same menstrual cycle.

Setting: Students were recruited in a college residence hall, and provided daily saliva samples to a researcher living nearby.

Patient(s): The 65 women who participated were all college students and ranged in age between 18 and 23.

Intervention(s): None.

Main Outcome Measure(s): Weight was assessed in the first week of the menstrual cycle and first week of the following menstrual cycle. Estradiol and progesterone were measured by radioimmunoassay in daily saliva samples.

Result(s): We did not detect a suppressive effect of weight loss on the overall level of either hormone. However, we did find evidence for more distinct follicular and luteal estradiol peaks in women who gained weight. Peak luteal progesterone also arrived about two days earlier in women who gained weight.

Conclusion(s): This finding adds to evidence that short-term response of ovarian function to weight loss young women is less pronounced than long-term response in older women.

Keywords: energy balance; weight change; estradiol; progesterone

INTRODUCTION

Substantial evidence shows that extended periods of moderate negative energy balance and elevated physical activity can suppress ovarian steroid output in later menstrual cycles (1-3). Effects of energy balance on ovarian function in premenopausal women are important both for understanding the evolution of the female reproductive system (4) and also potentially for the prevention of estrogen-dependent diseases that have been linked to Western lifestyles, especially endometrial (5) and breast cancers (6).

In addition to more established effects of long-term energetic stress, some previous research has also found that moderate, voluntary weight loss in mature women (25-40 years old) can immediately suppress concurrent luteal progesterone production (7). We investigated effects of voluntary weight loss or gain during a single menstrual cycle on profiles of estradiol and progesterone in the same cycle, of younger women.

MATERIALS AND METHODS

Participants and Measures

Sixty-five female college students participated in a study designed to test the effects of energy balance and psychological stress on ovarian function. We focus here only on the effects of energy balance as indicated by weight change. Their ages ranged from 18 to 23 (median = 20). None of the women had used oral contraceptives, and all reported having regular menstrual cycles prior to enrollment in the study. Although we cannot exclude to possibility of early pregnancy loss, all reported not having been pregnant about six months after the end of the menstrual cycle under study. The project was approved by Harvard University's Institutional Review Board. None of the authors has any conflict of interest relevant to this study.

Subjects were asked to collect saliva samples upon waking, for one complete menstrual cycle. Samples were collected directly into tubes pretreated with sodium azide, a preservative, and were stored at room temperature until being returned to the laboratory (8-10). We assayed estradiol only in samples collected over the last 20 days of the menstrual cycle, to ensure the presence of detectable levels. For the same reason, we also assayed progesterone in samples collected only over the last 14 days of the cycle. Of 1300 anticipated samples for assay of estradiol, 148 (11.4%) were missing. Of 910 samples anticipated for assay of progesterone, 111 (12.2%) were missing. One sample was excluded because its color suggested contamination. The remaining samples were either not collected by participants or not returned to researchers. There was no evidence that missing data were biased relative to reverse cycle day ($\chi^2_{19 \text{ df}} = 24.2$, $p = 0.19$) or cycle phase ($\chi^2_{1 \text{ df}} = 1.76$, $p = 0.18$).

Saliva samples were assayed for estradiol and progesterone using previously described methods (11). Each saliva sample and standard was run in duplicate. The empirical sensitivity limits were 4 pmol/L for estradiol and 13 pmol/L for progesterone. For estradiol, inter-assay coefficients of variation were 16% for high-hormone-concentration pooled saliva controls, 22% for low-hormone-concentration pooled saliva controls, and 17% and 11% for the two manufacturer-supplied controls (diluted 1:3). The intra-assay coefficient of variation was 10%. For progesterone, inter-assay coefficients of variation were 14% for high pools, 33% for low pools, and 23% and 8% for the two manufacturer-supplied controls (diluted 1:25 and 1:50, respectively). The intra-assay coefficient of variation was 9%.

Women were weighed to the nearest 0.1 kg using a single electronic scale (Tanita BF-350). Weights were recorded at the start of the menstrual cycle under study, and again within one week after the next menses. Weight change was taken as the difference between the two

measures. Other measurements, including waist and hip circumference and height, were also taken at before and after the menstrual cycle under study, and age were reported in a questionnaire.

Statistical Methods

We employed weight change as both a continuous variable and, at the suggestion of an anonymous reviewer, in three categories: weight loss greater than 0.5 kg, weight gain greater than 0.5 kg, or no change greater than 0.5 kg. We used ANOVA to test for differences in average estradiol and progesterone levels, and for differences in other factors, among the three weight change groups.

To further evaluate associations of weight change with estradiol and progesterone profiles, we employed linear mixed modeling. This technique allows for comparison of outcomes that vary over time, such as hormone levels. We used logged values of estradiol and progesterone because the distribution of each was right skewed. However, for the sake of clarity, we returned predicted values and standard errors from the log scale for display in Figures 1 and 2. To achieve smooth profiles, we modeled the effect of reverse cycle day on steroid hormone levels using polynomial terms as predictor variables: for estradiol, reverse cycle day (d), d^2 , d^3 , d^4 ; for progesterone reverse cycle day (d), d^2 , d^3 . We used four polynomial terms for estradiol in order to capture the expected two-peak profile, and three polynomial terms for progesterone. We modeled effects of weight change as a main effect plus interaction terms with reverse cycle day and powers of reverse cycle day. This approach allows weight change to be associated with complex differences in hormone profiles. The overall significance of differences in the pattern and level of hormone profiles can be tested with a likelihood ratio test. A significant likelihood ratio test in this context indicates that the overall hormone profile varies by weight change status.

Potential confounding factors were included as continuous covariates in the linear mixed models described above in the same way as weight change (i.e. main effect plus interactions with powers of reverse cycle day). We determined confounding if significant likelihood ratio tests became non-significant after the inclusion of the potential confounder.

RESULTS

Weight change ranged from a loss of 2.1 kgs to a gain of 4.3 kgs (median = -0.1 kgs). Of 65 women, 22 lost more than 0.5 kg, 25 maintained constant weight, and 18 gained more than 0.5 kg.

Table 1 compares women in each category of weight change. Significant differences were observed only for hip and waist circumference, which were larger at the start of the cycle among women who gained weight over the course of the cycle. Contrary to our predictions, we did not detect significant differences in average levels of either estradiol or progesterone. However, the power to detect differences, assessed post-hoc, was more limited than expected. Even to detect a one standard deviation difference, which in this study would reflect greater than 50% difference in average estradiol or progesterone levels, post-hoc power was less than 0.9.

However, weight change did predict significant differences in estradiol *profile* among these three categories (global test, $p < 0.01$), but did not reach significance when considering weight change as a linear predictor (global test, $p = 0.08$). There was also a significant interaction with the term for *reverse cycle day to the fourth power, d^4* (linear effect: $p < 0.01$, trichotomous effect: $p < 0.01$), indicating more distinct follicular and luteal estradiol peaks among women who gained weight, as can be seen in Figure 1.

We also detected significant overall differences in progesterone profile (linear effect: $p < 0.01$, trichotomous effect: $p < 0.01$), shown in Figure 2. In particular, the first order interaction between weight change and reverse cycle day was significant, indicating that peak progesterone occurred about two days later in the cycle among women who lost weight compared to women who gained weight. The associations described above remained statistically significant after controlling for potential confounding factors, including age, height, body mass index, hip and waist circumference, and cycle length.

DISCUSSION

Contrary to our expectation, there was no significant association of weight change with average levels of either estradiol or progesterone. While our findings did not fully accord with our expectations based on prior findings, there were some similarities. In particular, we note that, comparing profiles rather than absolute levels, women who gained weight had higher progesterone levels early in the luteal phase, whereas women who lost weight had higher progesterone later in the luteal phase.

Lager and Ellison (7) noted depression in levels of early luteal progesterone in cycles during which women lost weight, relative to cycles in which the same women gained weight. Comparing cycles within women may have given Lipson and Ellison (7) greater power to detect effects of weight loss than we enjoyed in this study. By comparing cycles in different women, we included error owing to differences in baseline hormone levels. Comparing cycles within women also reduces concerns about spurious associations owing to between-person confounding, because women are being compared to themselves. Instead, we attempted to identify confounding factors statistically, which is less preferred.

The tendency among women who gained weight to show a salivary estradiol profile with a distinct follicular peak may suggest higher fecundity. A rapid increase in mid-late follicular salivary estradiol has been associated with higher probability of conception (12). Again, comparisons across, rather than within, women may have limited our ability to detect expected effects on mean estradiol level.

A final possible explanation for the differences between our results and those of previous studies, especially Lager and Ellison (7), is that the women participating in this study were between 18 and 23 years old. Lager and Ellison (7) studied cycles in women with a mean age of about 29 years. Young women appear to have relatively depressed progesterone profiles (13), and may be less, rather than more, susceptible to subtle effects of negative energy balance than older women with robust menstrual cycles.

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FIGURE CAPTIONS

Figure 1. Weight change and salivary estradiol concentrations over the course of a menstrual cycle, predicted values and 95% confidence intervals a 4th order polynomial model.

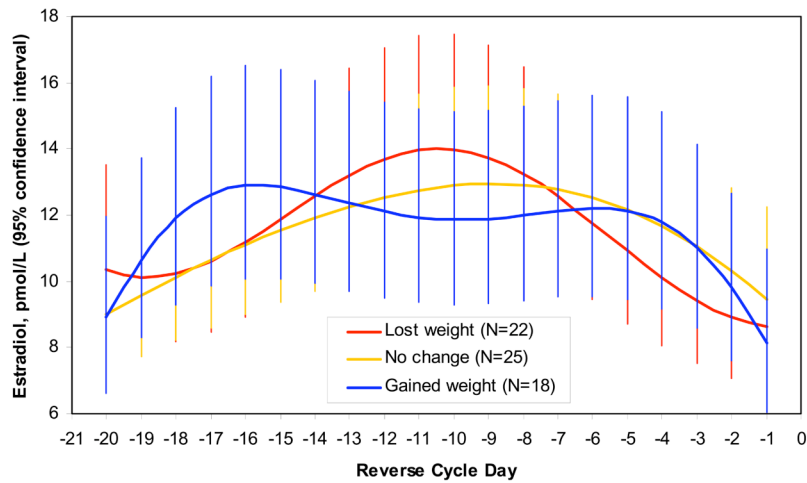


Figure 2. Weight change and salivary progesterone concentrations during the luteal phase, predicted values and 95% confidence intervals from a 3rd order polynomial model.

