#14: Increases in perceived stress during energy deficiency is associated with lower follicular phase estrogen exposure and distinguishes anovulation from less severe exercise-related menstrual disturbances in young women

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BACKGROUND: It is well documented that low energy availability and psychological stress can independently and in combination perturb reproductive function in mammalian species. Prolonged functional hypothalamic amenorrhea is associated with low and unchanging concentrations of estrogen and progesterone and alterations in stress and metabolic hormones. Clinical consequences include the development of the Female Athlete Triad, increased risk of injury, unfavorable changes in cardiovascular function, and transient infertility. While decades of research has documented the causal role of low energy availability, no studies have explored the possibility that psychological stress also contributes to reproductive dysfunction in exercising women. PURPOSE: To investigate the contribution of energy availability and psychological factors in the etiology of subclinical reproductive dysfunction induced by a three month exercise and caloric restriction intervention in sedentary, regularly menstruating women (n=36). METHODS: Women (age 18-24 yrs, BMI 21-29 kg/m2) were randomized to either an exercise only group or one of four groups with combinations of caloric restriction and exercise to induce varying levels of an energy deficit. The intervention occurred over the course of three menstrual cycles and included supervised exercise (5 d/wk, 50-85% VO2max, 20-75 min) with controlled feeding. Menstrual disturbances (luteal phase defects (LPD), oligomenorrhea, and anovulation (ANOV)) were detected using daily measures of urinary estrone-1-glucuronide (E1G), pregnanediol glucuronide (PdG), and mid-cycle luteinizing hormone, and menstrual calendars. Depressive symptoms were assessed at Baseline with the Beck Depression Inventory (BDI) (Beck, 1961), and Perceived Stress was measured every two weeks with the 14-item Perceived Stress Scale (Cohen, 1983). Subjects were divided into groups based on their change in perceived stress score from Baseline to the end of the intervention: Decrease in Perceived Stress -12.5 to -0.5; Low Increase in Perceived Stress 0.5 to 4.5; High Increase in Perceived Stress 5.0 to 36.5. The proportion of women in each Perceived Stress group who experienced at least one of each type of menstrual disturbance was determined along with effects of Perceived Stress group on urinary E1G and PdG. Logistic regression was used to detect associations between average energy deficit, Perceived Stress, and the induction of menstrual disturbances. Repeated measures ANOVA was performed to determine the effects of perceived stress on urinary E1G AUC and PdG AUC as calculated for each intervention cycle. RESULTS: The intervention caused moderate weight loss (0-4 kg), increases in fitness, declines in percent body fat and declines in luteal phase PdG exposure ($p<0.05$). Average percent energy deficit, changes in aerobic fitness, and changes in BMI across the intervention were not significantly different between the perceived stress groups. The average energy deficit, but not perceived stress, was associated with the incidence of a menstrual disturbance, particularly LPD ($p=.037$). The change in perceived stress, but not energy deficit, was predictive of those who experienced at least one anovulatory cycle ($p=0.021$). Specifically, High Increase in Perceived Stress was related to a higher incidence of ANOV vs. Decrease and Low Increase in Perceived Stress (High Increase, 58.3% vs. Low Increase, 14.3% and Decrease, 10.0%, $p< 0.013$). Low and High Increase in Perceived Stress were also associated with lower follicular phase E1G exposure ($p=.021$). BDI was not related to menstrual disturbances or urinary metabolites of reproductive hormones. CONCLUSION: Modest levels of caloric restriction and exercise induce subclinical luteal phase defects whereas increased psychological stress is associated with more severe disturbances, i.e., anovulation and reduced estrogen exposure in the context of energy deficiency. These results have implications for understanding individual susceptibility to exercise related menstrual disturbances. Future studies should address the reproducibility of this finding in a field setting and the underlying mechanisms of psychosocial determinants of menstrual disturbances.