Neuroendocrine recovery initiated by cognitive behavioral therapy in women with functional hypothalamic amenorrhea: a randomized, controlled trial

Vasiliki Michopoulos, Ph.D.,[a] Fulvia Mancini, M.D.,[b] Tammy L. Loucks, M.P.H., D.P.H.,[c] and Sarah L. Berga, M.D.[d]

[a] Department of Psychiatry and Behavioral Sciences, School of Medicine, Emory University, Atlanta, Georgia; [b] Service of Reproductive Medicine, Department of Obstetrics, Gynecology, and Reproductive Medicine, Institut Universitari Dexeus, Barcelona, Spain; [c] Department of Gynecology and Obstetrics, School of Medicine, Emory University, Atlanta, Georgia; and [d] Department of Obstetrics and Gynecology, School of Medicine, Wake Forest University, Winston-Salem, North Carolina

Objective: To determine whether cognitive behavior therapy (CBT), which we had shown in a previous study to restore ovarian function in women with functional hypothalamic amenorrhea (FHA), could also ameliorate hypercortisolemia and improve other neuroendocrine and metabolic concomitants of in FHA.
Design: Randomized controlled trial.
Setting: Clinical research center at an academic medical university.
Patient(s): Seventeen women with FHA were randomized either to CBT or observation.
Intervention(s): CBT versus observation.
Main Outcome Measure(s): Circulatory concentrations of cortisol, leptin, thyroid-stimulating hormone (TSH), total and free thyronine (T_3), and total and free thyroxine (T_4) before and immediately after completion of CBT or observation. (Each woman served as her own control.)
Result(s): Cognitive behavior therapy but not observation reduced cortisol levels in women with FHA. There were no changes in cortisol, leptin, TSH, T_3, or T_4 levels in women randomized to observation. Women treated with CBT showed increased levels of leptin and TSH, but their levels of T_3 and T_4 remained unchanged.
Conclusion(s): In women with FHA, CBT ameliorated hypercortisolism and improved the neuroendocrine and metabolic concomitants of FHA while observation did not. We conclude that a cognitive, nonpharmacologic approach aimed at alleviating problematic attitudes not only can restore ovarian activity but also improve neuroendocrine and metabolic function in women with FHA.
Clinical Trial Registration Number: NCT01674426. (Fertil Steril® 2013;99:2084–91. ©2013 by American Society for Reproductive Medicine.)
Key Words: Cognitive behavior therapy, cortisol, functional hypothalamic amenorrhea, reproduction, stress

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Reprint requests: Sarah L. Berga, M.D., Professor and Chairman, Department of Obstetrics and Gynecology, Associate Dean of Women's Health Research, Wake Forest School of Medicine, 1 Medical Center Boulevard, Winston-Salem, North Carolina 27157 (E-mail: sberga@wakehealth.edu).

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Functional hypothalamic amenorrhea (FHA) is a reversible form of anovulation. The proximate cause of FHA is reduced gonadotropin-releasing hormone (GnRH) drive, which manifests as reduced luteinizing hormone (LH) pulse frequency and reduced follicle-stimulating hormone (FSH) levels (1). Chronically reduced GnRH drive has been attributed to the combined effect of metabolic and psychogenic stresses (2–4). Indeed, women with FHA present with increased limbic-hypothalamic-pituitary-adrenal (LHPA) axis activation, as evidenced by elevated circulating and cerebrospinal fluid levels of cortisol (1, 5–7). Importantly, cortisol is not increased in women with other causes of anovulation (8). Additionally, women with FHA who spontaneously recover ovarian function display lower serum cortisol levels after recovery than women who have not recovered from FHA (8).

Our findings that women with FHA have increased LHPA activity, metabolic disturbances (1), and attitudes that compromise coping responses to stressors (2, 3, 9) led us to design a behavioral intervention targeted to improving problematic attitudes. As previously reported elsewhere, women with FHA were randomized to a 20-week program of cognitive behavior therapy (CBT) or observation, and their ovarian responses to intervention (CBT vs. observation) were gauged by determining the weekly levels of estradiol (E_2) and progesterone (P_4) before and after intervention (10). We found that CBT restored ovarian activity and ovulation in most subjects, but most women with FHA who were randomized to observation remained anovulatory (10). To extend our initial findings, we investigated whether CBT also would ameliorate other neuroendocrine and metabolic concomitants of FHA such as hypercortisolism and hypothyroidism.

Our previous research established that FHA is more than an isolated disruption of GnRH drive (1). Pharmacologic approaches include exogenous sex steroid administration if fertility is not immediately desired or ovulation induction if it is. However, neither approach corrects ongoing hypercortisolism and associated metabolic disturbances. Further, exogenous sex steroid administration may not fully prevent or reverse the health consequences associated with chronic stress and FHA such as osteopenia (11) and cardiovascular disease (12). There may be both maternal and fetal consequences to pregnancy in the presence of hypercortisolism and hypothalamic hypothyroidism (13–17). If CBT not only restored ovulatory ovarian function but also ameliorated neuroendocrine and metabolic concomitants of FHA, this would buttress the rationale for using CBT as a primary intervention.

The goal of the secondary analysis was to determine the extent to which CBT reversed neuroendocrine and metabolic concomitants of FHA, namely hypercortisolism, hypoleptinemia, and nonthyroidal illness. We hypothesized that CBT, but not observation, would lower cortisol levels in women with FHA, and that leptin levels and thyroid function would increase only in women with FHA treated with CBT.

MATERIALS AND METHODS

Patients

The institutional review board of Magee-Women's Hospital at the University of Pittsburgh approved the study protocol. The risks and benefits of study participation and alternative treatments were described verbally by the principal investigator and in the written consent document. Participants gave written informed consent before the study interventions. All participants completed the study. The diagnosis of FHA was established by excluding organic and other functional causes of anovulation and amenorrhea (1–3, 7, 8, 10). The inclusion criteria included an ideal body weight between 90% and 110% and a day-awake, night-rest schedule (10). The exclusion criteria were a psychiatric diagnosis, weight loss >10 lbs (>4.5 kg) within the last 5 years, and exercise >10 h/wk of any type or running more than 10 miles weekly. The exclusion of women with current or past psychiatric disorders, including eating disorders and drug dependence, was based upon the assessment tools described previously elsewhere (2, 3). Women with syndromal psychiatric conditions were referred for appropriate care and were excluded from participation. We used both interviews and inventories, including the Structured Interview for the Diagnostic and Statistical Manual of Mental Disorders IV, the Beck Depression Inventory, the Hamilton Rating Scale for Depression, the Dysfunctional Attitudes Scale, the Self-Control Scale, the Eating Disorder Inventory, and the Bulimia Test–Revised (7).

A provisional diagnosis of FHA was made if secondary amenorrhea persisted for more than 6 months, a urinary pregnancy test was negative, serum levels of luteinizing hormone (LH), FSH, thyroid-stimulating hormone (TSH), free thyroxine (T_4), and prolactin were within normal range, the LH:FSH ratio was less than 2, and no other identifiable cause of secondary amenorrhea, including polycystic ovary syndrome (PCOS), was identified (1–3, 7, 8, 10). None of the women with FHA displayed phenotypic or biochemical evidence of hyperandrogenism. Specifically, the levels of androstenedione, testosterone, dehydroepiandrosterone sulfate, and 17-hydroxyprogesterone were within accepted ranges (7).

Study Design

The women were randomized to either CBT or observation using a permuted block design that was administered by an independent statistician who communicated the randomization allocation to the study nurse. The physician in charge (S.L.B.), the master's level clinician, and the study coordinator were not blinded to the allocations. The research nurses who performed the General Clinical Research Center (GCRC) visits were blinded to the allocations, as were laboratory personnel who performed the hormone assays. Nine women were allocated to observation and eight to CBT (10). A crossover design was precluded because most of the women who recovered ovarian function remained recovered after CBT was completed. The women randomized to observation were offered CBT after their observation period. The CBT consisted of 16 sessions over a 20-week period (10). Sessions 1–6 of CBT focused on evaluating nutrition and exercise habits and attitudes toward nutrition and exercise (10). Sessions 7–12 identified maladaptive attitudes about stressors, exercise, nutrition, and weight, focusing on stress management techniques and adopting healthy attitudes (10). Sessions 13–16