Stress Induced Anovulation

S L Berga and T L Loucks
Emory University School of Medicine, Atlanta, GA, USA

Glossary

Allostasis	A sustained adjustment that promotes survival in response to chronic challenge; may increase long-term health burden.
Anovulation	The cessation of ovulation.
Cognitive-behavior therapy	A form of psychoeducation or talk therapy that addresses nonadaptive thoughts, cognitions, attitudes, and conceptualizations.
Eumenorrhea	A normal pattern of menstrual bleeding; can occur in the absence of ovulation.
Gonadotropin-releasing hormone (GnRH)	Decapeptide produced and released in a pulsatile mannner from hypothalamic neurons; stimulates the release of pituitary lutenizing hormone (LH) and follicle stimulating hormone (FSH).
Hypothalamic hypogonadism	A condition characterized by suppression of GnRH drive and, in turn, pituitary LH and FSH, resulting in reduced or absent gonadal steroidogenesis and gametogenesis.
Hypothalamic hypothyroidism	An allostatic adjustment in thyroidal function that conserves energy expenditure and is characterized by relatively normal levels of pituitary thyroid stimulating hormone (TSH) in the presence of suppressed levels of thyroid hormones triiodothyronine (T3) and thyroxine (T4).
Limbic-hypothalamic-pituitary-adrenal axis	Neuroendocrine circuit that mediates stress perception and stress responses.
Metabolism	Biochemical processes that regulate energy expenditure and storage.
Secondary amenorrhea	Cessation of menses in a woman of reproductive age who was previously eumenorrheic.
Stress	Physical and psychological stimuli that challenge the status quo and elicit homeostatic or allostatic behavioral responses.

Introduction

A wealth of scientific and clinical evidence supports the notion that stress causes reproductive compromise and increases health burden. Neuroendocrine, metabolic, and behavioral responses to acute stress represent transient homeostatic adaptations that promote survival in the face of perceived challenge; chronic stress elicits allostatic (sustained) adjustments that also promote survival but at greater health cost (Figure 1). Reproductive compromise impedes population replenishment and increases acute and chronic health burden in women, men, and children due to metabolic dysfunction, obesity, diseases of aging, preterm delivery, birth defects, costly and risky infertility therapies, and, through epigenetic mechanisms, it imprints the next generation. Stress is the most common and most commonly underappreciated cause of reproductive dysfunction (Table 1). Stress-induced anovulation (SIA), often termed functional hypothalamic amenorrhea (FHA) or functional hypothalamic chronic anovulation, causes infertility and increases acute and chronic health burden.

Behaviors that chronically activate the limbic-hypothalamic-pituitary-adrenal (LHPA) axis and/or chronically suppress the hypothalamic-pituitary-thyroidal (HPT) axis compromise the hypothalamic-pituitary-gonadal (HPG) axis in both women and men by reducing hypothalamic gonadotropic-releasing hormone (GnRH) drive. Individuals with functional (not due to defined organic conditions) forms of hypothalamic hypogonadism typically engage in a combination of behaviors in response to psychogenic stress that concomitantly induce intermittent or chronic energy imbalance. Further, chronic adrenal activation may increase the energetic cost of common activities such as running. In women, functional hypothalamic hypogonadism exists on a spectrum that includes polymenorrhea (menstrual interval < 24 days), eumenorrhea with reduced luteal progesterone secretion, and anovulatory eumenorrhea, oligomenorrhea (menstrual interval 735 days), or amenorrhea (absence of menstruation for >3–6 months). In men, oligoasthenospermia (very low sperm count with low motility and abnormal morphology) may result, but this is typically not clinically evident unless fertility is being sought or severe testosterone deficiency results in muscle wasting or other phenotypic alterations.

This article focuses primarily on SIA/FHA in women. SIA/FHA typically results from psychogenic stress coupled with a mild energy imbalance and represents an allostatic adaptation, that is, a stable

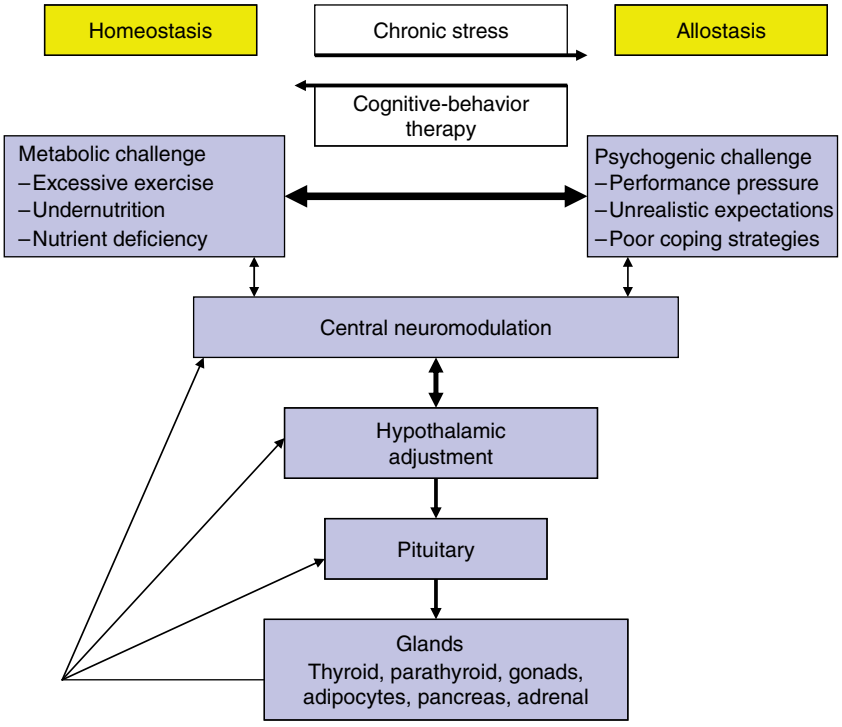

Figure 1 Conceptualization of synergism between metabolic and psychogenic stress in the pathogenesis of stress-induced anovulation.

Table 1 Common causes of anovulation/amenorrhea[a]

	Percentage
Stress-induced anovulation/ functional hypothalamic amenorrhea	34
Hyperandrogenism/PCOS	29
Hyperprolactinemia	13
Premature menopause	12
Asherman's syndrome	5
Other	7

[a]Based on data presented in Reindollar, R. H., Novak, M., Tho, S. P. T., et al. (1986), Adult-onset amenorrhea: a study of 262 patients, *American Journal of Obstetrics and Gynecology* **155**, 531–543. PCOS, polycystic ovarian syndrome.

change in behaviors and secretory patterns that promotes acute survival but at some health cost. SIA/FHA affects roughly 5% of women of reproductive age; less severe forms of hypothalamic hypogonadism are more common and are less clinically evident (Figure 2).

Stress-induced anovulation is theoretically reversible, but reproductive recovery appears to depend on the restoration of eucortisolemia and at least partial recovery from functional hypothalamic hypothyroidism. Hormone replacement strategies have limited benefit for women with SIA/FHA because they do not promote recovery from allostatic endocrine adjustments in the adrenal and thyroidal axes. Indeed, the rationale for the use of sex steroid replacement is based on the erroneous assumption that functional forms of hypothalamic hypogonadism represent only or primarily a loss of sex steroid exposure due to reduced GnRH drive. Further, the replacement of sex hormones masks deficits that accrue from chronically altered adrenal and thyroidal functions. Long-term deleterious consequences of SIA/FHA probably include an increased risk of cardiovascular disease, osteoporosis, depression, other psychiatric conditions, dementia, and neurodevelopmental compromise in offspring. Although fertility can be restored with exogenous administration of gonadotropins or pulsatile GnRH, fertility management alone does not engender adrenal and thyroidal recovery. Pregnancy in the face of ongoing psychogenic stress and metabolic imbalance may increase the likelihood of poor obstetrical, fetal, or neonatal outcomes. In contrast, behavioral and psychological interventions that address problematic behaviors and attitudes have the potential to facilitate reproductive recovery along with adrenal and thyroidal recovery. In short, full endocrine recovery offers better individual, maternal, and child health.

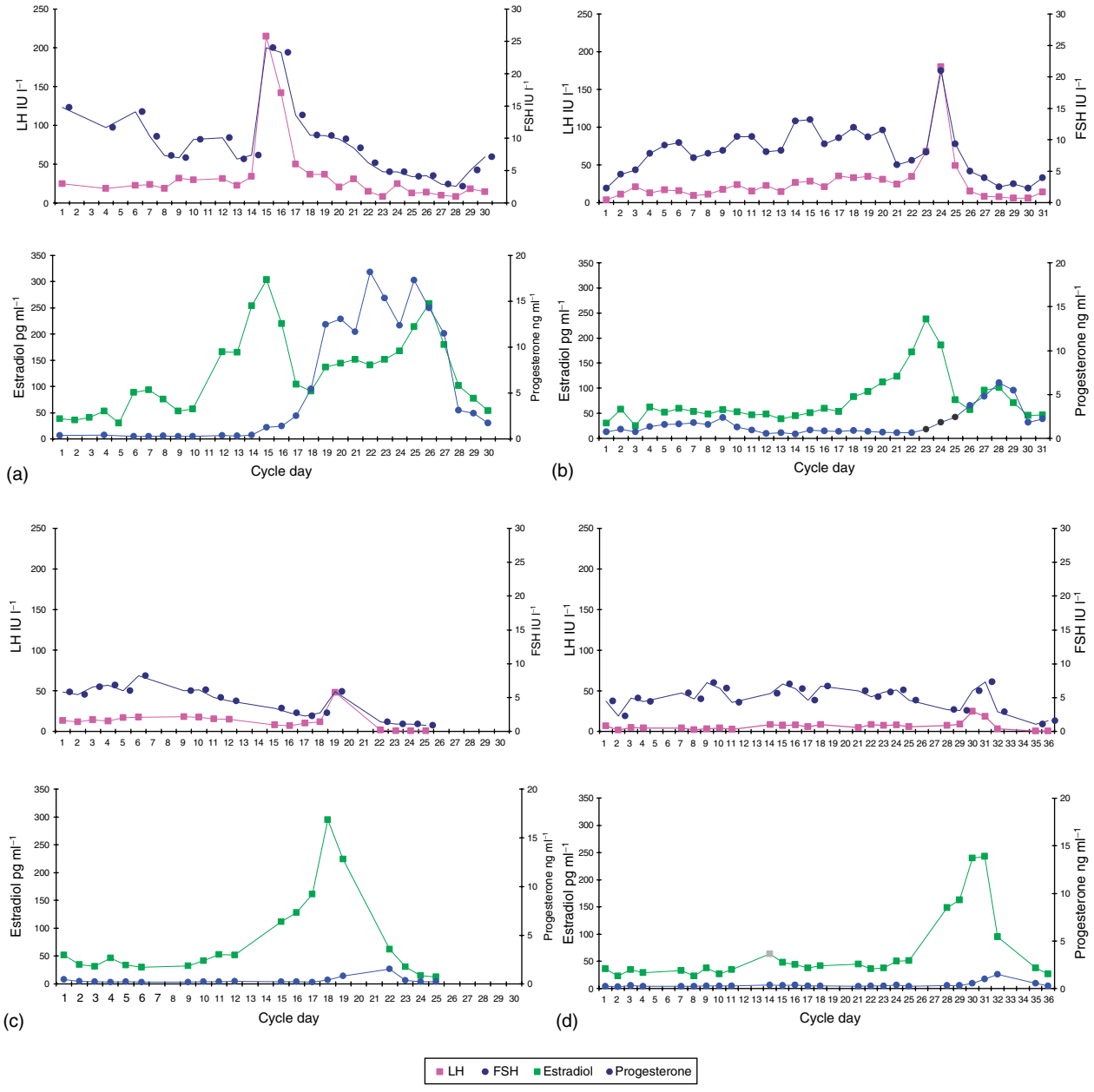

Figure 2 Continuum of ovarian function in women with preserved menstrual cyclicity. a, Ovulatory eumenorrhea; b, luteal insufficiency; c–d, eumenorrheic anovulation. Pituitary gonadotropin (LH and FSH) and ovarian sex steroid (estradiol and progesterone) levels were obtained daily for one cycle. FSH, follicle-stimulating hormone; LH, luteinizing hormone. Note that FSH > LH, but FSH < 20 IU/L, thus the cause of hypogonadism is hypothalamic rather than reduced ovarian reserve.

Neuroendocrine Mechanisms Linking Cognition, Mood, Behavior, and Gonadotropin-Releasing Hormone Drive

Our conceptualization of the bidirectional interaction between behavior and gonadal function has been refined by scientific insights into the mechanisms mediating neuroendocrine responses to thoughts, feelings, and behaviors.

The proximate cause of hypothalamic forms of hypogonadism, including SIA/FHA, is reduced hypothalamic GnRH input. Gonadal function depends directly on secretion from the hypothalamus of GnRH as pulses. Declines in pulsatile GnRH secretion reduce pituitary secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) and wholly or partially compromise folliculogenesis.

Decreased GnRH drive is a common cause of anovulation and amenorrhea. Decrements in central GnRH–LH/FSH drive exist on a continuum, however, and may vary from day to day. Because of this potential variability in GnRH drive, ovarian compromise exists on a spectrum and may present as polymenorrhea, eumenorrhea, oligomenorrhea, or amenorrhea. Clinically, the decreased ovarian function can be occult or obvious. In men, decreased central GnRH drive may cause oligoasthenozoospermia. Typically, gonadal compromise in men is clinically occult unless fertility is sought and the compromise is sufficiently significant to cause infertility. However, severe hypothalamic hypogonadism in men may present as decreased libido, diminished muscle mass, or altered hair (beard) growth.

The most common cause of reduced GnRH drive is functional; that it, it is not due to identifiable organic causes such as hypothalamic tumors or pituitary adenomas. Functional hypothalamic hypogonadism can be defined as a common and theoretically reversible form of gonadal compromise in which psychophysiological responses to life events activate central neural networks and thereby alter glandular secretion and metabolism.

The mechanisms mediating the disruption of central GnRH drive are poorly understood and complex. GnRH neurons are diffusely distributed in the medial basal hypothalamus. Most, but not all, GnRH axons project to the median eminence, allowing pulses of GnRH to be released into the portal vasculature. GnRH neurons communicate with one another via synapses. Although GnRH neurons are endogenously pulsatile, their activity must be synchronized by GnRH-to-GnRH synapses for the GnRH bolus released into the portal vasculature to be of sufficient magnitude to trigger pituitary release of LH and FSH. GnRH neurons receive synapses from neurons that contain GnRH, the endogenous opioid peptide β-endorphin, neuropeptide Y (NPY), and catecholamines. Other factors that modulate the frequency or activity of the GnRH pulse generator are thought to exert their effects indirectly by acting through the neuronal systems that have direct synaptic connections or by interacting with glial cells that interpose between synapses. For instance, progesterone appears to slow the frequency of pulsatile GnRH release by increasing hypothalamic opioidergic tone, but it also may cause glial cells to envelope the GnRH neurons and to reduce thereby the GnRH-to-GnRH connections. Peripheral substances may gain access to the GnRH neuronal network via specialized neurovascular cells that line the fenestrated blood–brain barrier at the level of the hypothalamus and median eminence, so the modulation of GnRH secretion is not confined to central factors. The brain–gut axis appears to communicate the metabolic status of an individual to the hypothalamic GnRH neurons through multiple mechanisms. A partial list of putative neuromodulators of GnRH drive is shown in Table 2.

Table 2 Putative modulators of GnRH drive[a]

CRH	Metabolic signals
Opioids	Sex steroids
Adrenergic	Gonadal peptides
GABA	Growth factors
Dopamine	Glial cells
Serotonin	GnRH
Immune	Other

[a]CRH, corticotropin releasing hormone; GABA, γ-aminobutyric acid; GnRH, gonadotropin-releasing hormone.

Progress has been made in quantifying endocrine patterns for research purposes. However, in humans, GnRH pulsatile secretion can be inferred only from the pattern of LH secretion in the circulation. Blood samples must be obtained via an indwelling intravenous catheter at intervals of 10–15 min for durations of 12–24 h. Even so, inherent limitations exist in estimating GnRH secretion from peripheral LH patterns. The tedious nature of quantifying central GnRH drive explains why this is not done routinely during clinical evaluation. Technical limitations also plague the recognition and quantification of stress and metabolic status. The accuracy of psychometric inventories for assessing and quantifying stress, mood, and cognitive patterns is inherently constrained by reporting biases, whereas endocrine or biophysical indices of stress and metabolic status are technically cumbersome and expensive to collect. Neuroimaging techniques have afforded a new window into the neurochemistry and neuroanatomy of behaviors and thoughts, but these techniques have not yet been used to understand the pathogenesis of stress-induced reproductive compromise.

Although innumerable animal studies have demonstrated that activation of the hypothalamic-pituitary-adrenal (HPA) axis by a variety of stressful paradigms induces reproductive compromise, only a few studies have elucidated the mechanisms mediating the disruption of GnRH drive. Direct evidence exists for corticotropin releasing hormone (CRH), β-endorphin, dopamine, and arginine vasopressin. Recently, NPY has been implicated as serving a neuromodulatory link between metabolic deficits induced by diet and exercise and reduced GnRH drive. A key inhibitory neurotransmitter system in the brain uses γ-aminobutyric acid (GABA). GABA opens the same potassium channels in neurons of the mediobasal

hypothalamus as μ-opioid receptor agonists such as β-endorphin. GABA inhibited GnRH gene expression in rats and suppressed pubertal GnRH increase in juvenile female rhesus monkeys, but the role of GABA in human hypothalamic hypogonadism remains unclear. Serotonin neurons may also play a role in modulating GnRH drive.

Pathogenesis of Stress-Induced Anovulation

The best biochemical evidence supporting the concept that stress impairs ovarian function in women is the consistent demonstration that women with hypogonadotropic hypogonadism not due to defined organic conditions have higher cortisol levels than eumenorrheic, ovulatory women. There is direct evidence that this relationship holds in women with athletic amenorrhea as well. In a study by Loucks et al., an inverse relationship was observed between the degree of ovarian compromise and cortisol levels. When compared with eumenorrheic but sedentary women, eumenorrheic athletes had less luteal progesterone secretion, as evidenced by lower urinary levels of pregnanediol-glucuronide, fewer LH pulses in a day, and higher cortisol levels. Furthermore, amenorrheic athletes that were anovulatory had the fewest LH pulses in a day and the highest cortisol levels despite comparable levels of exertion and fitness. An inverse relationship holds between adrenal activation (independent of the life events or behaviors that initiate or sustain this activation) and suppression of the hypothalamic GnRH drive to the ovary, as evidenced by marked reduction in LH pulse frequency.

Other hypothalamic outputs also are altered in women with SIA/FHA. Given the neuroanatomical integration of the hypothalamus, this is predictable. The purpose of the hypothalamus is to generate an endocrine action plan to preserve the organism in the face of challenge. Part of the action plan involves metabolic mobilization. However, metabolic mobilization involves more than an increase in cortisol secretion. In SIA/FHA, the thyroid axis differs from that of eumenorrheic women in that thyrotropin (TSH) is not increased in response to decrements in thyronine and thyroxine, which indicates an altered hypothalamic set point akin to what is seen in hospitalized patients who develop what is referred to as sick euthyroid syndrome. In athletic women, a similar alteration in the thyroid axis was seen only in those who had compromised ovarian function. The secretory patterns of growth hormone, prolactin, and melatonin also differed from those of eumenorrheic women. The constellation of neuroendocrine aberrations that accompany SIA/FHA strongly suggests that central neurotransmission has been chronically altered to forge an allostatic state. The aim of allostatic adjustments is to allow the individual to cope with chronic as opposed to acute challenge. In this context, then, the hypothalamus links the external environment, the internal milieu, and gonadal function.

The process of recovering from the allostatic state of SIA/FHA is also interesting but less well documented. We showed that women in the process of recovering from functional hypothalamic hypogonadism displayed cortisol levels identical to those of eumenorrheic women before there was complete recovery of GnRH drive. Further, a marked increase in thyrotropin-stimulating hormone (TSH) drive occurred as a prelude to increases in thyroxine and thyronine. We recently reported that women with SIA/FHA treated with cognitive-behavior therapy (CBT) displayed a return of ovarian function and ovulation and reduced cortisol levels but had only partial recovery from hypothalamic hypothyroidism and no weight gain. These data, coupled with our psychometric data showing that women with SIA/FHA differ from eumenorrheic women (EW) in their attitudes toward eating and desire for thinness, raise the possibility that intermittent or mild energy imbalance may persist after CBT-induced reproductive recovery. In short, hypothalamic recovery involves a set of interlinked readjustments, including LHPA restoration, return of GnRH pulsatility, and at least partial remission of hypothalamic hypothyroidism, but the duration and sequence of recovery is just now beginning to be described and the role of metabolic factors as mediators of recovery remains unclear.

The characteristic hypothalamic alterations associated with SIA/FHA only become problematic when ongoing challenges elicit a chronic rather than acute response. The long-term consequences of persistent HPA activation have been studied in animal models and hippocampal neuron loss has been documented. Stress appears to increase the risk of dementia and other neurodegenerative disorders. Other long-term sequelae of persistent metabolic mobilization are largely unknown, but there is no reason to assume that such a process is benign. For instance, recent data obtained in women with weight-restored anorexia nervosa who remained amenorrheic indicated that exogenous sex steroid replacement was unable to stimulate appropriate bone accretion. The investigators speculated that the ineffectiveness of hormone exposure was due to ongoing metabolic derangements such as increased cortisol exposure, altered growth hormone action, or hypothalamic hypothyroidism. Because of the concomitant endocrine and metabolic disturbances, hypothalamic hypogonadism must be regarded as a condition deserving

clinical attention even when fertility is not an immediate goal.

The central neuromodulators responsible for the initiation and maintenance of the disruption of GnRH are difficult to identify in humans. First, the factors that initiate allostasis may differ from those that maintain allostasis. To study initiating factors, we would need to intensely monitor populations at risk for the development of hypothalamic hypogonadism or try to induce hypothalamic hypogonadism in a nonhuman primate model. Once a chronic hypogonadal state had been reached, it theoretically would be possible to identify the agents that maintain this disruption by administering antagonists that cross the brain–blood barrier, by performing lumbar punctures and obtaining cerebrospinal fluid (CSF), or by performing neuroimaging studies with an appropriate ligand. To date, efforts to identify these neuromodulators in humans have yielded inconsistent results. Thus, naloxone, an opioidergic blocker, increased LH pulse frequency or levels in some, but not all, women with SIA/FHA. Also, the infusion of metoclopramide, a dopamine receptor blocker, to women with FHA accelerated LH pulse frequency, whereas that of eumenorrheic women remained constant. These data suggest that there may be dopaminergic as well as opioidergic inhibition of GnRH drive. To explore the hypothesis that the reduction in GnRH drive was maintained by CRH, vasopressin, β-endorphin, or a combination of these factors, we performed lumbar punctures to obtain rostral CSF in women with SIA/FHA and those with eumenorrhea. This approach revealed increased CRH in the CSF of women with depression, but we found that CRH levels were identical in women with SIA/FHA and eumenorrhea. Vasopressin levels were similar, but, surprisingly, β-endorphin levels were lower in women with SIA/FHA. Further, we evaluated free cortisol in the CSF of these same women and found that these levels were approximately 30% higher in those women with stress-induced anovulation. In aggregate, these findings (Figure 3) support the notion that the preservation of CSF CRH levels in the presence of elevated CSF cortisol reflects chronic stress-induced (allostatic) resistance to negative feedback suppression by cortisol.

Other putative central neurotransmitters that may contribute to the initiation and maintenance of SIA/FHA are the serotonergic and GABAergic systems. Several lines of evidence suggest that serotonergic function gates stress reactivity and metabolism. First, we showed in our monkey model of SIA/FHA that stress-sensitive monkeys had larger cortisol elevations and reduced prolactin responses to fenfluramine, a serotonergic agonist. These data were interpreted as indicating that central serotonergic

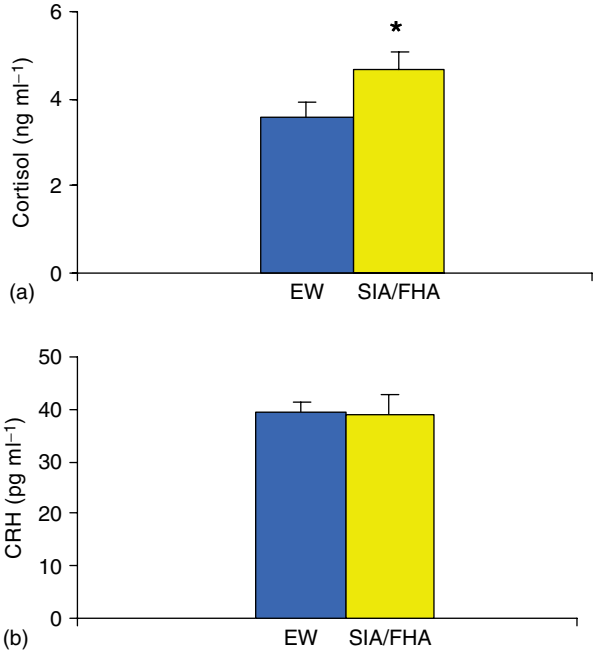

Figure 3 Mean ± SE cerebrospinal fluid hormone levels in eumenorrheic women (EW) and women with SIA/FHA, demonstrating allostatic resistance to cortisol feedback suppression of CRH. a, Cortisol levels; b, CRH levels. CRH, corticotropin releasing hormone; SIA/FHA, stress-induced anovulation/functional hypothalamic amenorrhea. From Brundu, B., Loucks, T. L., Adler, L. J., et al. (2006), Increased cortisol in the cerebrospinal fluid of women with functional hypothalamic amenorrhea, *Journal of Clinical Endocrinology and Metabolism* **91**, 1561–1565.

tone was reduced in stress-sensitive as contrasted with stress-resilient monkeys. Second, serotonergic neurons, which express leptin receptors, terminate on GnRH neurons. Serotonin has satiety effects similar to those of leptin and may modulate the response to orexigenic and anorectic signals. Moenter's lab exposed fasting female mice to saline, leptin, or fluoxetine, a selective serotonin reuptake inhibitor (SSRI) antidepressant, and followed estrus cycle length. Leptin and fluoxetine prevented fasting-induced cycle lengthening, whereas the serotonin receptor antagonist metergoline blocked cycle rescue by fluoxetine. Treating leptin-deficient *ob/ob* and leptin receptor-deficient *db/db* mice with fluoxetine did not normalize body weight or rescue estrus cycles. Further, there is abundant evidence of a role for the serotonergic system in the regulation of stress reactivity and feedback inhibition of the HPA axis by cortisol. In addition, variation in transporter-facilitated uptake of serotonin has been implicated in anxiety in humans and in animal models of anxiety and stressfulness. Human serotonin reuptake transporter (SERT) gene transcription is modulated by a common

polymorphism in its upstream regulatory region. The short variant reduces the transcriptional efficiency of the SERT gene promoter, resulting in decreased SERT expression and serotonin reuptake. The short (s) variant polymorphism is associated with an increased incidence of affective disorders in humans and maladaptive behavior in monkeys coincident with increased HPA responsivity to stress. Further, the long/short genotype produces a phenotype similar to that of the short/short genotype. In humans, the SERT polymorphisms moderated the influence of stressful life events on depression in a representative birth cohort. Stress-sensitive monkeys had a lower expression of SERT mRNA and monoamine oxidase A (MAO-A) in the caudal region of the dorsal raphe nucleus, whereas no differences were detected between stress-sensitive and stress-resilient monkeys in the mRNA for the serotonin 1A autoreceptor or MAO-B. The determinants of stressfulness in women with SIA/FHA are incompletely understood, and this is certainly one of the variables that warrants further investigation.

Judd et al. reported that a single 2 mg dose of alprazolam, a GABA receptor agonist, decreased cortisol levels and increased LH pulse frequency from 0.8 to 2.0 pulses/8 h in women with stress-related anovulation, whereas its administration decreased LH pulse frequency in eumenorrheic women in the follicular phase. These data also suggest a possible indirect role for GABA neurons in the stress-induced neuromodulation of GnRH pulsatility. Not surprisingly, the neurochemistry of stress and SIA/FHA is far from simple, and firm mechanistic conclusions are not possible at present.

Behavioral, Nutritional, and Metabolic Influences on the Reproductive Axis

Identification of factors that activate the adrenal axis and suppress the thyroidal and ovarian axes can be challenging. It has been suggested that different stressors and behaviors activate somewhat different central mechanisms, such that the signals that alter hypothalamic function are specific to the type of stressor. Indeed, this variability may well explain in part why the neurochemistry of stress is so complex. Psychosocial dilemmas are seen as activating those central pathways subserving perception, whereas exercise and weight loss are generally viewed as disturbing metabolic regulation. Although it seems logical that specificity in the neural or peripheral cascades mediating responses to specific stressors exist, we currently have no method for clearly delineating psychogenic from metabolic stress. Psychogenic stress has a metabolic cost and metabolic stressors, such as food restriction and excessive exercise, are often initiated to cope with psychogenic stress. However, until proven otherwise, the safest assumption is that stress comes in flavors and that some individuals are more sensitive than others to the same stressor or set of stressors.

Behavioral Influences

A number of behavioral and other psychogenic factors including exercise, low weight and weight loss, affective and eating disorders, various personality characteristics, drug use, and external and intrapsychic stresses have been associated with functional hypothalamic hypogonadism. Given individual variation in metabolism, autonomic tone, habitus, aptitudes, attitudes, and psychological valences, what is stressful to one person may be more or less so to another. Therefore, it is not surprising to find behavioral heterogeneity in the pathogenesis of SIA/FHA. Any given stressor, when the dose is large enough, can probably activate the central neural pathways leading to the disruption of GnRH. In clinical research, the trend has been to study single stressors and to partition as separate populations women with exercise amenorrhea, anorexia nervosa, and idiopathic amenorrhea. Populations studied in clinical research settings may not be entirely representative of all women with SIA/FHA because research subjects must meet relatively strict inclusion and exclusion criteria. In general, women with SIA/FHA do not report or do not have an easily identified solitary stressor. Typically, there are multiple, seemingly minor, stressors, such as a combination of job or school pressures, poor eating habits, and increased energy expenditure through activity or exercise.

To understand the role of psychological variables, such as attitudes and expectations, in the pathogenesis of SIA/FHA, we compared three groups of women: those with eumenorrhea and demonstrable luteal adequacy; those with SIA/FHA unrelated to excessive exercise, weight loss, an eating disorder, drug use, or an affective disorder; and those with anovulation due to an identifiable organic cause. Being amenorrheic, regardless of cause, was associated with a compromised sense of psychological equilibrium as reported on psychometric inventories, but, as a group, only women with SIA/FHA differed from the other groups on scales that measured unrealistic expectations and dysfunctional attitudes (defined as attitudes likely to impair coping responses). For instance, women with SIA/FHA were both highly perfectionistic and sociotrophic (having a high need for social approval). Because perfectionism interferes with social approval or acceptance, one interpretation is that the concomitant high drive for perfectionism and sociotrophy

creates an intrapsychic conflict that women with SIA/FHA may not possess the appropriate coping skills to resolve. Another interpretation is that the expectation of simultaneously being perfect and garnering social approval is an unrealistic expectation of self and others. Our earlier study suggested that women with SIA/FHA had trouble relaxing and having fun, attributes that may further predispose them to value performance at the expense of psychological needs. Although women with SIA/FHA do not typically meet the criteria for an eating disorder, they display many attitudes and behaviors similar to women with eating disorders, such as a drive for thinness and disordered eating. What appears to separate women with undifferentiated SIA/FHA from those with an eating disorder is the degree of disturbance, including the degree of food restriction, weight loss, binging, and perfectionism. However, direct comparisons have not been conducted for any of these psychological attributes, so these interpretations are based on impressions from extant literature. The bottom line is that attitudes and expectations engender behaviors such as aberrant food intake and excessive exercise that further challenge the hypothalamus to maintain homeostasis. Whether the identifiable behavior is performance pressure, exercise, or irregular food intake, the end result is the same, that is, the disruption of the GnRH pulse generator to the extent that anovulation occurs. It stands to reason, then, that the key to recovery is to change both the behaviors and attitudes that have initiated and now sustain reduced GnRH drive. Once the hypothalamic GnRH pulse generator has been disrupted, it may take a prolonged duration of energy balance and improved psychological equilibrium for the hypothalamic allostasis to reverse and for ovulatory function to return.

The available data suggest that any behavior or expectation that concomitantly activates to a sufficient degree the HPA and HPT axes has the potential to disrupt the GnRH pulse generator. Thus, the list of behaviors and attitudes associated with the development of SIA/FHA is expected to be diverse and extensive. Generally, a mix of multiple, seemingly minor psychogenic and metabolic stressors appears to be more deleterious to reproductive function than a solitary stressor.

Nutritional and Metabolic Influences

Nutritional and metabolic signals play critical roles in the elaboration of homeostatic and allostatic responses to ongoing challenges and can influence the reproductive system at many levels. Research on overnutrition has focused primarily on specifying its effects on gonadal function, with some attention having been given to the secondary consequences of obesity on endometrial development and central hypothalamic drive. Few studies have characterized the role of nutritional signals in the modulation of reproductive function in men, but available evidence suggests that undernutrition is as deleterious to reproductive competency in men as it is in women.

Metabolic imbalance occurs when energy expenditure exceeds energy intake (negative energy balance). The brain is the most metabolically active tissue in the body, requiring 16 times more energy per unit mass than muscle tissue. Because humans have much bigger brains relative to body size than do other primates or other species, they use more of their daily energy intake than any other species to supply their brain; humans are estimated to use 25%, monkeys 8%, and rodents 5%. Indeed, as a species, humans may be uniquely sensitive to energy imbalance. Metabolism reflects the interactions of the neuroendocrine system (e.g., HPA and HPT axes), body composition (adipokines), and the enteric system (insulin, ghrelin, etc.). Given the multitude of redundant metabolic and nutritional signals communicating energy status to the brain, it is difficult to specify the independent role of any one factor or signal. Signals reflecting energy stores, recent nutritional information, and specific classes of nutrients are integrated in the central nervous system, particularly the hypothalamus, to coordinate energy intake and expenditure. Chronic energy deficiency alters thyroidal function to slow metabolism and correct negative energy balance. Food intake is influenced by availability, emotional state, social cues, and learned behaviors. Although peripheral signals convey information about energy stores and immediate energy availability to the hypothalamus, particularly the arcuate nucleus, these two categories of signals are not exclusive. For instance, leptin and insulin, which are actively transported across the blood–brain barrier, potentiate satiety signals. Thus, the level of any one signal *per se* may be less important than the action of that hormone, and the action is likely to be gated by the constellation of other metabolic signals. Putative orexigenic signals include ghrelin, NPY, orexins A and B, melanin-concentrating hormone (MCH), and agouti-related peptide. Putative anorectic and satiety signals include (but are not limited to) cortisol, CRH, insulin, glucose, resistin, leptin, proopiomelanocortin (POMC), cocaine- and amphetamine-regulated transcript (CART) peptide, peptide YY (PYY), and glucagon-like peptide (GLP)-1. Adipokines (adipocyte-derived hormones) implicated in energy regulation include leptin, adiponectin, and resistin. Leptin is the dominant long-term energy signal informing the brain of adipose

energy reserves; it also functions as a satiety signal. Adiponectin acts as an insulin-sensitizing agent by reducing hepatic glucose production and is reduced in obesity. Resistin is linked to insulin tolerance and decreases glucose uptake by adipocytes. Ghrelin, a 28-amino-acid acylated hormone that is also a growth hormone secretagogue, is produced by the gastrointestinal tract, especially the fundus of the stomach. Plasma ghrelin levels rise during fasting and immediately before anticipated mealtimes and then fall within an hour of food intake, suggesting that ghrelin is important for meal initiation. Given the plethora of nutritional and metabolic signals, specifying their independent effects is challenging, particularly in humans.

Relevant human studies on the role of these factors in reproduction are few. Depression, like stress, involves LHPA axis dysregulation and is associated with loss of appetite; resistin levels correlated with free cortisol levels and adiponectin correlated with insulin sensitivity in a study of depressed humans. In a rodent model, the central LHPA axis challenge of hypoxia and the LHPA axis feedback challenge of dexamethasone independently decreased body weight and increased adiponectin levels, whereas dexamethasone, but not hypoxia, increased resistin. In women, ghrelin levels were reported to be increased in anorexia nervosa and exercise amenorrhea. However, Troisi et al. observed lower ghrelin in women with anorexia or bulimia that correlated with serum cortisol levels. In these studies, subjects and controls differed markedly with regard to body weight and leptin levels, food intake was not assessed, and the diurnal pattern of ghrelin was not determined; for instance, De Souza et al. and Tanaka et al. obtained only a single morning's blood sample after an overnight fast and Misra et al. determined ghrelin levels only overnight. Of note, Miljec et al. reported ghrelin insensitivity in response to an infusion of ghrelin in women with anorexia nervosa compared to eumenorrheic women, but appetite was measured only by self-report and not by food intake. Women with SIA/FHA are more active than most eumenorrheic women and tend to consume less fat and more carbohydrates, but reproductive recovery from SIA/FHA did not require weight gain and was not associated with a change in standard metabolic variables such as leptin.

A balance between energy intake and expenditure is critical to survival. Every action, even thinking, has an energetic cost. Given the fundamental nature of metabolism, it is not surprising that organisms have evolved a complex and redundant signaling system to gate appetite, food-seeking behavior, and fuel storage. Although stress increases energetic demand, the acute behavioral response is often a blunting of appetite and a reduction in food intake so as to shift attention away from maintenance/sustenance needs and toward coping responses. Chronic reductions of appetite and energy intake in the face of an increase in energy demand probably represent appetite or metabolic allostasis; because of ensuing hypothalamic hypothyroidism, undernutrition may develop without weight loss. The exact mechanisms subserving the multiple associations between reproduction and nutrition and the applicability of animal studies to human syndromes remain to be determined. Given the considerations outlined here, including the high metabolic demands of the human brain, energetic imbalance may have more serious reproductive consequences for humans than for other animals.

Psychological states generate metabolic demands. Psychological states recognized as stressors activate the LHPA axis. When this activation is acute and limited, the adrenal releases a bolus of cortisol, a hormone with multiple metabolic properties. If the stressor is chronic and mild to moderate, then there is modest activation of the LHPA such that cortisol is mildly elevated but the circadian pattern of cortisol is preserved. With extreme unremitting stress, cortisol secretion is elevated and there is loss of the circadian pattern. Conditions that chronically activate the LHPA axis have been associated with a spectrum of reproductive impairment.

In summary, there is a plethora of metabolic signals that reflect the acute and chronic nutritional state of a given individual. These signals convey information to important tissues and organs and thereby engender homeostatic and allostatic responses. A key target tissue is the brain. Both undernutrition and overnutrition impact reproductive processes. Given the energetic demands of reproductive processes, however, undernutrition has the potential to induce more significant reproductive compromise.

Synergism among Stressors

The notion that stress comes in neurochemical flavors is supported by animal studies suggesting that there are subtle but distinct differences in the neuroendocrine responses to different stress paradigms. Further, neuroendocrine and metabolic responses to acute exercise were greater in men whose HPA axis did not suppress when they were given dexamethasone before the exercise challenge. These data indicate that the degree of HPA activation potentiates the neuroendocrine and metabolic responses to subsequent challenge. Conversely, Altemus et al. showed that lactating women are hyporesponsive to exercise challenge. Taken together, these data buttress the

notion that responses to a given stressor are gated not only by the stressor type but also by host factors, including hormonal and metabolic states. Thus, some individuals are clearly more reactive to similar stressors than others. Obviously, emotional valence and expectations also determine the extent to which psychosocial variables serve as a psychogenic stressors. Our preliminary investigations in women who developed SIA/FHA unrelated to weight loss, exercise, and definable psychiatric disorders indicated that a primary factor that distinguished women with SIA/FHA from those with definable causes of anovulation and those who were ovulatory was the presence of unrealistic expectations. Fioroni also found that women with SIA/FHA, compared to eumenorrheic women or those with other causes of anovulation, held more negative attributions about recent life events. Kirschbaum found that men who did not habituate when exposed to repeated psychogenic challenge viewed themselves as less attractive, had lower self-esteem, and reported being in a depressed mood more often. Apparently, unachievable ambitions or other cognitive distortions create vulnerability to life's inevitable challenges and probably heighten responsivity to metabolic stressors such as exercise or food restriction. Potentially, the converse is true. Energetic imbalance may augment reactivity to psychogenic stressors.

There can be no doubt that weight loss and exercise serve as metabolic stressors. In monkeys trained to run, it was shown that caloric supplementation reversed the anovulation induced by training. Interestingly, the monkeys did not spontaneously develop a compensatory increase in appetite and had to be bribed with colorful candy to consume more calories. On the other hand, modest dietary restriction accompanied by small amounts of exercise greatly increased the proportion of monkeys who become anovulatory when presented with social stress. A prospective study of unselected women demonstrated that exercise and weight loss caused anovulation. It is likely that sufficient exercise and weight loss, independent of psychogenic stress, can alter metabolism to the point that GnRH pulsatility is disrupted. Loucks and Thurma quantified the amount of energy restriction needed to impact GnRH drive by studying eumenorrheic women in the follicular phase. Energy balance was achieved by providing 45 kcal/kg of lean body mass (LBM)/day. Graded daily energy deficits of 10, 25, and 35 kcal/kg were then experimentally induced for 5 days. An energy deficit of 33% had no impact on LH pulse frequency, whereas an energy deficit of approximately 75% induced a decline in LH pulse frequency of approximately 40%. The induction of an energy deficit resulted in a graded increase in the 24-h cortisol level. At an energy availability of 10 kcal/kg of LBM (75% deficit), the mean 24-h cortisol was increased by approximately 30%, which is the amount of increase typically seen in women with SIA/FHA. Much like stress-sensitive monkeys, women whose luteal phase progesterone levels were lowest at the initiation of the energy restriction showed the greatest response to the imposed metabolic challenge. In most real-life situations, except for extreme circumstances such as war or famine, metabolic deficits are not imposed but, rather, initiated by individuals in response to self-imposed expectations including drive for thinness. Most women with SIA/FHA, when carefully evaluated, display more than one trait, state, or behavior capable of activating stress response cascades or inducing a mild metabolic deficit, but most do not have a profound metabolic deficit that alone would explain the reduction in central GnRH drive. Many of the behaviors, such as exercise, that independently suppress central reproductive drive but only at more extreme levels, may be initiated as coping responses to psychosocial dilemmas. Because of the synergism between metabolic and psychogenic stressors, a combination of multiple, small magnitude, mixed stressors may be potentially more disruptive of reproductive function than a single large stressor limited to one category.

To better understand how a combination of seemingly minor psychogenic and metabolic stressors might synergistically disrupt GnRH drive as demonstrated in our monkey model, we compared endocrine responses to submaximal exercise in women with SIA/FHA to those in eumenorrhea. Women with SIA/FHA displayed a larger increase in cortisol than ovulatory eumenorrheic women in response to exercise. Further, glucose responses between the two groups were divergent in that women with SIA/FHA showed a 10% decrease in glucose whereas eumenorrheic women had a modest 3% increase in glucose, presumably to cope with the energetic demand of exercise. Interestingly, these two groups did not differ at baseline with regard to cortisol or glucose levels. The decrement in glucose seen in SIA/FHA but not eumenorrheic women suggests latent metabolic compromise and indicates that SIA/FHA women are unable to meet energetic demands of ongoing activities. Further, it is likely that the drop in glucose activates the HPA axis and is at least partly responsible for the sustained hypercortisolemia characteristic of SIA/FHA. Because metabolic signals modulate GnRH pulsatility, exercise-induced metabolic imbalance also probably contributes to ongoing reproductive suppression. These results also reveal why the endocrine effects of a stressor, such as exercise, depend on the preexisting neuroendocrine and metabolic state of the individual.

Treatment Considerations

SIA may not be recognized unless the menstrual interval is markedly short, long, irregularly irregular, or absent. Likewise, luteal phase insufficiency due to decreased hypothalamic drive may not be noted unless infertility results. Even then, luteal insufficiency is notoriously difficult to document unless it is recurrent. Based on the foregoing concepts, we speculate that the more clinically evident the ovarian compromise, the greater is the hypothalamic challenge and the more profound are the associated adrenal and thyroidal derangements and sex steroid deprivation.

If a woman with functional hypothalamic hypogonadism is seeking to become pregnant, ovulation induction can be accomplished technically with the exogenous administration of pulsatile GnRH therapy or gonadotropins. The administration of exogenous GnRH therapy is advantageous insofar as it diminishes the risk of ovarian hyperstimulation and multiple gestation associated with gonadotropins. Clominphene citrate is an option, but it may be less effective because of its hypothalamic site of action and the hypothalamus of women with SIA/FHA is already not responding to decreased sex steroid secretion. Concerns have been raised that ovulation induction may place women with SIA/FHA at increased risk for premature labor and intrauterine growth restriction. The parenting skills of women with SIA/FHA may be impaired because they are already overwhelmed and stressed prior to pregnancy and delivery and their psychological precariousness may place their children at risk for poor psychosocial development. Further, a recent study showed that children born to mothers with clinically occult hypothyroidism due to autoimmune thyroiditis had a mean full-scale intelligence quotient that was seven points lower than the control population. The women with clinically silent hypothyroidism had a 30% reduction in thyroxine, which is roughly what is observed in women with SIA/FHA. Of critical importance is the fact that maternal thyroxine is the only source of fetal thyroxine in the first trimester and the predominant fetal source in the second and third trimesters. Because the fetal brain requires an appropriate amount of thyroxine for neurogenesis, even small deficits in thyroxine may induce neurodevelopmental deficits. Increased maternal cortisol may also have independent effects on fetal neurodevelopment and organogenesis. Recent evidence showed that severe stress, such as that associated with the unexpected death of a child, increased the risk of congenital anomalies of the cranial neural crest eightfold. Further, stress and its endocrine concomitants and even brief undernutrition have been implicated as a cause of preterm delivery. It is not known if the endocrine concomitants associated with SIA/FHA pose a similar risk, but this is clearly a potential hazard if ovulation induction is undertaken before amelioration of the allostatic changes in the adrenal and thyroidal axes.

A popular approach to a woman with SIA/FHA who is not seeking immediately to become pregnant is to offer her hormone replacement. This approach is based on the presumption that sex steroid deprivation is the primary therapeutic issue. There are inherent limitations with this approach, however. First, data indicate that exogenous sex steroid exposure does not fully promote bone accretion or cardioprotection in the presence of ongoing metabolic derangements. Second, the ongoing insults to the brain from chronic amplification of stress cascades go unchecked. Further, estrogen therapy does not correct hypothalamic hypothyroidism. In short, hormone therapy may mask potentially deleterious processes that are unlikely to be ameliorated by hormone exposure alone. It is critical to remember that SIA/FHA is more than a disorder of reduced GnRH secretion.

Hormone therapy *per se* is unlikely to be harmful, but more than hormone administration is needed – the stress process needs to be interrupted. Although psychopharmacological approaches have not been well studied, they probably could be used on an interim basis in special circumstances. The study by Judd suggested that a short course of alprazolam might be effective in reducing HPA activation and permitting hypothalamic-pituitary-ovarian (HPO) recovery. However, this approach is not recommended for a woman hoping to conceive. The optimal intervention is to reverse the stress process so that the hypothalamus recovers and gonadal function resumes. An integral goal of the treatment plan for women with functional hypothalamic hypogonadism is to help them identify and ameliorate the sources of psychogenic and metabolic stress and to provide emotional support while they learn coping mechanisms other than dieting or exercising. Nonpharmacological interventions such as stress management, relaxation training, or psychoeducation empower individuals by fostering self-care and competency. In this regard, nonpharmacological therapies have the potential to produce long-term benefits on psychological and, thereby, physical health. Behavioral therapies acknowledge the wisdom of the body and understand that SIA/FHA represents an endocrine adaptation that can be reversed with appropriate psychogenic and behavioral modifications.

Given these considerations, we recently studied whether CBT aimed at ameliorating problematic attitudes and behaviors facilitated ovarian recovery in

normal weight women with SIA/FHA. Women with SIA/FHA were randomly assigned to observation versus CBT groups. CBT consisted of 16 visits with a physician, therapist, or nutritionist during 20 weeks. The two groups were followed for return of menses for up to 8 weeks following the intervention. Regardless of menstrual pattern, estradiol and progesterone levels were monitored at weekly intervals for 4 weeks before and after observation or CBT. Approximately 88% of those who underwent CBT had evidence of ovulation, whereas only 25% of those in the observation group did. Figure 4 illustrates the recovery of sex steroid secretion in a woman in the CBT group who showed ovarian recovery and in a woman in the observation group who did not have recovery of ovarian function. Interestingly, when it occurred, ovarian recovery was not associated with significant weight gain. This does not mean that subjects did not alter food intake or energy expenditure, however. Improved nutrition generally restores the thyroidal

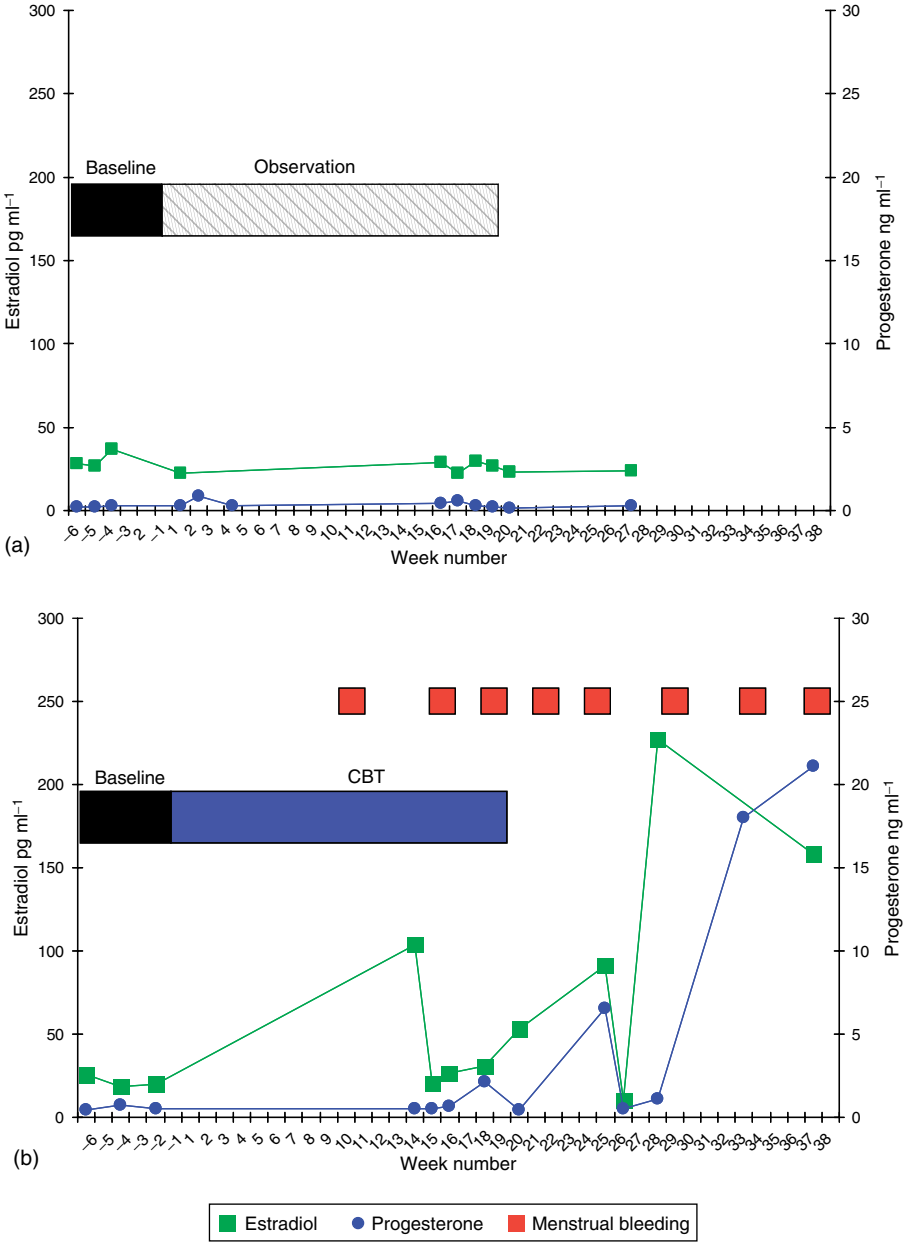

Figure 4 Serum estradiol and progesterone levels and menstrual bleeding in women with SIA/FHA. a, A patient who was observed and did not recover; b, a patient who was treated with cognitive-behavior therapy and recovered. CBT, cognitive-behavior therapy; SIA/FHA, stress-induced anovulation/functional hypothalamic amenorrhea. From Berga, S. L., Marcus, M. D., Loucks, T. L., et al. (2003), Recovery of ovarian activity in women with functional hypothalamic amenorrhea who were treated with cognitive behavior therapy, *Fertility and Sterility* **80**, 976–981.

axis, thereby leading to an increased basal metabolic rate and a need for more calories. Our earlier studies showed that women who experienced a spontaneous recovery from SIA/FHA were eucortisolemic, had increased but not fully restored LH pulsatility, and markedly increased TSH levels in the face of persistent reductions in T_3 and T_4 levels. We recently compared metabolic variables in women who did and who did not recover from SIA/FHA after CBT intervention and observed that ovarian recovery was associated with a decline in cortisol and increase in TSH but that thyroidal hormones and leptin levels were comparable between recovered and unrecovered women. Taken together, these findings suggest that the thyroidal axis, which gates metabolic tone, remains restrained by an as yet uncharacterized factor(s) after HPA and HPO recovery or recovers more slowly than the HPA and HPO axes, similar to the recovery timeline related to acute illness. Ultimately, behavioral and psychological interventions that address problematic behaviors and attitudes permit the resumption of ovarian function along with recovery of the LHPA and HPT axes. In short, full endocrine recovery offers better individual, maternal, and child health.

Summary

Stress is one of the most common and most commonly underappreciated causes of infertility and reproductive compromise in men and women. Stress-induced hypothalamic hypogonadism increases the acute and chronic health burden for individuals and their offspring. Our findings regarding the pathogenesis of SIA/FHA reveal a powerful synergism between metabolic imbalance and psychogenic challenge and underscore that seemingly mundane psychological issues evoke not only reproductive compromise but also concomitant neuroendocrine and metabolic allostasis. These mechanistic pathobiological insights have been harnessed to develop therapeutic options aimed at ameliorating the sustaining cognitive and behavioral variables. By showing that CBT reverses SIA/FHA, we can appreciate the inherent neural plasticity that forms the rationale for coupling mindfulness approaches with the judicious use of psychopharmacological and technical interventions.

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See Also the Following Article

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Stress Management and Cardiovascular Disease

D Lane
Sandwell and West Birmingham Hospitals NHS Trust, Birmingham, UK
D Carroll
University of Birmingham, Birmingham, UK

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Glossary

Angina pectoris	Chest pains, often radiating to the arms, shoulders, and jaw, arising from reduced blood flow to the heart as a result of coronary atherosclerosis.
Angiography	A technique for measuring the extent of coronary atherosclerosis.
Atherosclerosis	An accumulation of fatty deposits causing hardening and narrowing of the arteries.
Cardiac rehabilitation	A combination of lifestyle education, exercise, and, increasingly, stress management training directed at patients suffering from coronary heart disease. The aim of cardiac rehabilitation is to facilitate physical, psychological, social, and emotional recovery.