CENTRAL CAUSES OF AMENORRHEA

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ABSTRACT
Normal ovulatory menstrual cycles reflect a coordination of an intact hypothalamic-pituitary-ovarian unit. This process involves neuroendocrine messaging between the hypothalamus, pituitary, and gonads. Common central causes of amenorrhea include functional hypothalamic anovulation, exercise-associated anovulation, pharmacologic-induced anovulation, psychiatric associated disorders such as anorexia nervosa and bulimia, and genetic-developmental defects of the gonadotropin releasing hormone (GnRH) neuronal unit. While brain radiation, trauma or a congenital deficiency of gonadotropins can certainly result in amenorrhea, many more common subtle factors can also effect this pathway. Neuroendocrine regulation of ovulation involves the interaction between neurons secreting GABA, kisspeptin, and neurokinin which modulate the function of GnRH neurons. There is also a link between the reproductive axis, nutritional-energy balance status, and dysregulation of two key peptides, leptin and ghrelin, that occurs when there are extreme, nutritionally stressful conditions such as with anorexia nervosa, extreme exercise, or starvation. In the evaluation of patients with central amenorrhea, the history and physical are crucial to determine the laboratory evaluation and if brain imaging is required. Understanding the patient's goals will allow an individualized treatment regimen, as it will likely differ if the patient desires children imminently. For complete analysis of this and all areas of Endocrinology, please visit our FREE web-textbook, www.endotext.org.

Introduction
The hypothalamic-pituitary-ovarian axis must be fully synchronized for normal ovulation and successful reproduction. Factors that modulate hypothalamic gonadotropin hormone releasing hormone (GnRH) include pubertal maturation, alterations in energy balance, body composition and metabolism, and stress and emotional changes. Disruption of normal menstrual cycles and normal ovulation are often associated with a variety of life style factors such as excessive exercise, nutritional deprivation, and psychological stress. In the vast majority of cases, this is associated with normal neuroanatomic findings. In a small subset, neuroendocrine abnormalities such as isolated gonadotropin deficiency (Kallmann syndrome), head trauma, radiation effects, Sheehan syndrome, and pituitary apoplexy are identified (see Table 1). Regardless of the etiology, the final common pathway is a change in the normal pattern of episodic secretion by the GnRH pulse generator resulting in disruption of ovulation and amenorrhea. These types of disorders will be discussed in this chapter.

Table 1. Classification of Anovulation Associated with the CNS Hypothalamic-Pituitary System

Functional Hypothalamic Anovulation
• Exercise-related factors • Nutritional factors • Psychogenic or stress factors
Physiologic Anovulation
• Prepubertal phase • Postpartum phase • Breastfeeding phase
Pharmacologic-Associated Anovulation
• Opiate agonist • Dopaminergic agonist
Psychiatric-Associated Disorders
• Pseudocyesis • Anorexia nervosa • Bulimia
Organic Defects of the Hypothalamic-Pituitary Unit
• Kallmann syndrome • Isolated gonadotropin deficiency • Pituitary tumors • Sheehan syndrome • Pituitary apoplexy/aneurysm • Empty sella syndrome • Inappropriate prolactin secretion • Infection (human immunodeficiency virus, tuberculosis) • Head trauma • Post-radiation effects

NEUROENDOCRINE CONTROL OF GNRH SECRETION DURING THE REPRODUCTIVE CYCLE

Prior to the existence of laboratory techniques to assess gonadotropin secretion, physicians relied on clinical judgement to arrive at the diagnosis of central amenorrhea (1). The advent of the radioimmunoassay in the late 1960s paved the way for a laboratory diagnosis of this disease. The secretion of endogenous GnRH is difficult to assess in the human because this decapeptide is rapidly metabolized within 2 to 4 minutes in the peripheral circulation. Thus, it is not possible to directly assess GnRH secretion and the majority of clinical investigations utilize frequent measurements of LH concentrations as the surrogate marker for hypothalamic GnRH secretion. In women with regular menstrual cycles, clinical studies have demonstrated a characteristic pulsatile secretion of LH at a frequency of 90-120 minutes during the follicular phase and a frequency of 180-240 minutes during the luteal phase (2). Small alterations in LH pulsatile frequency and or amplitude can result in a range of disorders including luteal phase defects, oligo-ovulation and anovulation. Thus, most studies have examined for changes in LH pulsatile frequency and amplitude as the major endpoint in studies to investigate functional hypothalamic amenorrhea.

Puberty

Normal female pubertal development requires an elaborate orchestration of the hypothalamic-pituitary-gonadal axis. Prepubertal girls have low LH, FSH, and estradiol. Prepubertal girls respond with a rise in gonadotropin secretion (predominantly FSH) in response to exogenous GnRH administration (3). This response indicates that the hypothalamic GnRH pulse generator is less active during this period of development. At pubertal onset there is a distinct diurnal variation as the gonadotropins rise (4). Although the exact triggers at the time of puberty are poorly understood, there are three distinct changes that are observed in the hypothalamic-pituitary unit (5).

1. A nocturnal sleep-related augmentation of pulsatile LH secretion begins as a result of the increase in GnRH pulsatility.
2. The sensitivity set point of the hypothalamus to estradiol and testosterone decreases, thereby resulting in an increased basal gonadotropin secretion.
3. In the female, a positive feedback capability develops, and critical levels of estradiol can trigger a large release of GnRH, and subsequently LH, leading to ovulation.

Central axis control of gonadotropins

The effect of estradiol on the CNS is generally dichotomous. While E2 sensitizes the pituitary gonadotrophs to GnRH by inducing GnRH receptor expression, it also suppresses the release of GnRH from the hypothalamus (6). This "negative feedback" is the dominant effect of estradiol for the vast majority of the ovulatory cycle. The negative control of gonadotropin release is augmented by inhibin secreted from ovarian granulosa cells. Unlike other endocrine systems, continued exposure to higher levels of estradiol (>250 pg/mL) for prolonged duration (>48hours) produced by the dominant ovarian follicle results in a sudden release of a GnRH-LH surge termed "positive feedback" that triggers ovulation at midcycle (7).

Neuroendocrine regulation of ovulation

During embryogenesis in primates, the GnRH cells migrate from the nasal placode into the bilateral arcuate nuclei in the mid-hypothalamus. The neurons of the arcuate nucleus that target the GnRH cells synapse with incoming axons from extrahypothalamic brain areas such as the amygdala, hippocampus, and cortex that target the GnRH cells. Conceptually, these interneuronal connections release excitatory (E) or inhibitory (I) neurotransmitters. Variations in the synaptic balance of these neurotransmitters exist during the ovulatory cycle. During negative feedback, the E/I ratio is low and during positive feedback the E/I ratio is high (8). Gamma amino isobutyric acid (GABA) neurotransmitters are primarily associated with inhibitory GnRH activity, while kisspeptin and neurokinin are associated with excitatory GnRH activity (9). Estradiol effects on GnRH pulsatility appears to be mediated by altering the E/I ratio through synaptogenesis and synaptolysis of neuronal pathways targeting GnRH secretion (10). During the bulk of the cycle (negative feedback) the effect of E2 is synaptogenic and induces neurotransmitters with a net inhibition of GnRH secretion. In

contrast, during the pre-ovulatory phase (positive feedback), estradiol triggers synaptolysis, thereby causing the ovulatory surge.

Kisspeptins are G protein-coupled receptor ligands originally identified as human metastasis suppressor gene products that have the ability to suppress melanoma and breast cancer metastasis. These peptides have recently been found to play an important role in initiating the secretion of GnRH at puberty (11). Kisspeptin, encoded by the *KISS1* gene is located on the long arm of chromosome 1 (1q32) and is a peptide consisting of 145 amino acids. In the brain, the gene is transcribed within the hippocampal dentate gyrus and activates the G protein-coupled receptor GPR54.

In 2003 the discovery of the necessary role kisspeptin has in puberty led to the understanding of the neuroendocrine effect on human reproduction (12). The GnRH neurons of primates, rodents and sheep are found in close apposition with kisspeptin neurons. GnRH neurons express the kisspeptin receptor, and when kisspeptin is incubated with hypothalamic explants, it stimulates the release of GnRH. This effect is not observed in kisspeptin receptor knockout mice. While GnRH neurons show an increase in firing rate *in vitro* following kisspeptin treatment, this effect is attenuated by the application of a kisspeptin receptor antagonist. The discovery of inactivating mutations in the kisspeptin/GPR54 further ascertained its role in human reproduction. In humans, inactivating GPR54 mutations are associated with normosmic hypogonadotropic hypogonadism while activation of GPR54 signaling is associated with precocious puberty. Central and peripheral administration of kisspeptin stimulates the hypothalamic-pituitary-gonadal axis while pre-administration of a GnRH antagonist abolishes this effect. Collectively, these observations strongly suggest that kisspeptin can be a primary mediator for activation of GnRH neurons.

All of the current studies initiating puberty with exogenous kisspeptin were performed on monkeys and rodents; however, one study demonstrated return of reproductive hormone production in women with hypothalamic amenorrhea who received twice-weekly kisspeptin injections for 8 weeks (13). Another potential clinical application for kisspeptin is to use it as a trigger for the LH surge during ovulation induction for in vitro fertilization (IVF). It has been shown to effectively induce oocyte maturation, and may be a more physiologic mechanism for inducing ovulation than hCG, which is currently used for ovulation induction. There is speculation that a kisspeptin trigger may also decrease the risk for ovarian hyperstimulation syndrome; however, studies comparing kisspeptin and a GnRH agonist need to be completed prior to recommending the use of kisspeptin (14). Further studies are ongoing to further establish the role of kisspeptin in restoring reproductive function in certain conditions.

Modulation of GnRH Secretion by Opioidergic, Dopaminergic, and Excitatory Amino Acids

Animal studies have shown that other neurotransmitter systems such as dopamine, norepinephrine, and serotonin can regulate GnRH or LH secretion. These studies suggest that activation of the noradrenergic system is associated with increased release

of GnRH whereas dopaminergic or serotonergic activation can either inhibit or stimulate GnRH release (15-21). These observations can explain in part the CNS-associated disruption of normal menstrual cycles in patients who take phenothiazine (dopamine receptor antagonists), stimulants, antidepressants, and sedatives on a chronic basis.

Excitatory amino acids such as glutamate and aspartate have been shown to be localized to the arcuate nucleus in the media basal hypothalamus adjacent to GnRH neurons and have been implicated in a regulatory role for GnRH secretion primarily during pubertal maturation (22). These two amino acids appear to activate GnRH secretion during puberty in monkeys.

Endogenous opiates peptides such as endorphins, enkephalins, and dynorphins appear to play largely an inhibitory role in GnRH and LH secretion. The same functional neuronal network that secretes kisspeptin also co-secrete dynorphin, and collectively it is known as the kisspeptin-neurokinin B-dynorphin (KNDY) pathway (23). KNDy neurons in the infundibular/arcuate nucleus have an effect on GnRH by influencing both the GnRH cell body and the neurosecretory terminals. Given the KNDy cells express both neurokinin B receptors and the kappa opioid peptide receptor (dynorphin receptor), it is suspected that the stimulatory role of neurokinin B and the inhibitory role of dynorphin work together to cause a pulsatile release of kisspeptin, which results in a GnRH pulsatile release (24). In patients with hypothalamic amenorrhea, blockade of endogenous opiate receptors with the receptor antagonists such as naloxone or naltrexone (dynorphin antagonists) will induce an increase an increase in pulsatile release of GnRH and LH (25). Long term treatment of hypothalamic amenorrhea patients with naltrexone can result in return of normal menstrual cycles in some individuals (26). These findings indirectly suggest that endogenous opiate activity is suppressing GnRH secretion. The use of an inhibitory neurotransmitter may be beneficial in patients who require a suppression of GnRH or LH secretion. For example, patients with PCOS generally have a dysregulation of gonadotropin secretion which likely contributes to irregular ovulation may benefit from exogenous regulation of the opiate peptides (27).

LINKAGE BETWEEN NUTRITIONAL STATUS AND HYPOTHALAMIC AMENORRHEA

For many years, clinicians have sought to identify the functional link between nutritional status and reproduction. Recent identification of neuropeptides that alter feeding behaviors has provided a physiological mechanism to explain the shutdown of the H-P-O axis for individuals who experience significant changes in nutritional status (i.e. starvation and obesity). Two key peptides, leptin and ghrelin have been identified and appear to regulate feeding behavior which may mediate the dysregulation of the reproductive axis under extreme, nutritionally stressful conditions.

Leptin is a 16 Kd, 167 amino acid polypeptide that was first isolated in 1994. This peptide is a product of the *ob* gene. Based on phylogenetic studies, leptin is conserved and has been identified in amphibians, rat, sheep, and human (28). Leptin is primarily produced by the adipocytes but has also been shown to be synthesized in other tissues

such as skeletal muscle, heart, stomach, and the placental-fetal unit. Leptin is a member of the cytokine family and is classified as an anorexigenic peptide. Other peptides in this class include pro-opiomelanocortin and the cocaine and amphetamine-regulated transcription peptides. Leptin's action is opposed by orexigenic peptides such as neuropeptide Y and the agouti-related peptide.

Leptin is known to circulate in two forms: as a free form and as a bound form complexed to soluble leptin-binding proteins or to circulating leptin receptors. Physiological studies demonstrate that leptin is secreted in a pulsatile manner with a diurnal rhythm. Current commercial assays for leptin appear to measure total leptin in the serum compartment. Transport of leptin into the brain has been described as unidirectional through the blood brain barrier into brain tissue.

For patients with HA, most studies report a decrease in total circulating leptin with a loss of the normal diurnal rhythm (29). This lower leptin level is a common characteristic of several energy-deficient conditions and is associated with a decrease of the LH pulse frequency. There have now been six receptor isoforms described for leptin. These receptors have been localized to the brain, ventral hypothalamus, lung, kidney, pancreas, adrenals, ovaries, skeletal muscle, and hematopoietic stem cells. Within the brain, the arcuate nucleus appears to have the greatest concentrations of leptin receptors (as well as GnRH receptors).

Binding of leptin to its receptor causes functional dimers to form and activates the *JAK/STAT3* intracellular signaling pathways. The effects of leptin on GnRH release may be mediated through kisspeptin. The leptin receptor (Ob-Rb) is not expressed by GnRH neurons of the hypothalamus. However Ob-Rb mRNA is found in 40% of Kiss1 mRNA-expressing cells of the arcuate nucleus (30). The expression of *Kiss1* mRNA in the mutated leptin receptors is reduced in comparison with wild-type mice. Furthermore, the expression of *Kiss1* mRNA has been shown to be influenced by nutritional status. In pre-pubertal rats, which have been food deprived for 72 h, the hypothalamic expression of Kiss1 mRNA is markedly reduced (31).

In contrast to leptin, ghrelin, another energy-balance peptide, was found to be elevated in individuals with HA. Ghrelin is a 28-amino acid orexigenic peptide that was first isolated in the stomach and is a potent stimulus to GH release. In the fasting state, ghrelin serves as the hunger signal from the periphery to the CNS, acting on the hypothalamic arcuate nucleus, a region which is known to control food intake. Based on these relationships, it is tempting to rationalize that leptin and ghrelin simply serve as natural on/off switches for regulation of feeding behavior.

Functional Hypothalamic Amenorrhea

A practical definition of functional hypothalamic amenorrhea (HA) is the absence of menstrual cycles for more than 6 months without evidence of anatomic or organic abnormalities (32). Three main types of functional hypothalamic amenorrhea have

been recognized, associated with stress, weight loss, or exercise (33). Other more serious organic disorder can mimic HA such as isolated gonadotropin deficiency (see table 1). Thus, this diagnosis should be made after exclusion of other causes.

HA is associated with increased cortisol secretion that reflects increased activity of the hypothalamic-pituitary-adrenal (HPA) axis (34). There appears to be an increased secretion of a "stress response complex" of hormones such as CRH, ACTH, cortisol, PRL, oxytocin, vasopressin, norepinephrine, and epinephrine (TABLE 2). CRH has been shown to directly inhibit GnRH secretion in rats, monkeys, and humans at the hypothalamic level in *in vitro* and *in vivo* experimental models. This inhibition can be negated by administration of a CRH receptor antagonist or by naloxone, an opiate receptor antagonist. Taken together, these observations suggest that the inhibitory effect of CRH is mediated in part by increased opioidergic activity.

The increased secretion of ACTH at the pituitary level may also suppress pituitary response to GnRH. In addition, increased cortisol levels may also dampen pituitary response to GnRH. It must be emphasized that an acute stress response will be unlikely to alter ovulatory function since the H-P-O axis is quite resilient. On the other hand, it appears that chronic environmental stressors lead to long term activation of the HPA axis which in turn can induce ovulatory dysfunction at either the hypothalamic or the pituitary level.

Modification of the stress response can restore normal HPO function. The validation for this comes from evidence of complete resumption of normal ovulatory function in women with HA treated with cognitive behavioral therapy (CBT) (35). Treated women exhibited increased LH pulsatility and decreased cortisol levels. A similar study at the same institution found that CBT resulted in an increase in leptin and TSH levels, and improved the neuroendocrine and metabolic components of HA (36). This provides evidence that stress-reducing behavioral changes may be successful in restoring normal ovulation and metabolic function in women with HA.

A constellation of other neuroendocrine alterations occur in HA. There is a suppression of the hypothalamic-pituitary-thyroid axis with a resultant decrease in circulating thyroid hormones (37). There also may be a decrease in prolactin secretion as well as alterations in other neurohormones such as melatonin (38). There may be difficulties in recognizing the stressors that have elicited the stress response in FHA since the stressors may not be objective or quantifiable (39). Human stressors often reflect attitudes of self or society. Subjective stressors such as these may not be as easy to quantitate as stressors with objective measures such as food deprivation or outright violence.

Evaluation

The American Academy of Pediatrics and the American College of Obstetricians and Gynecologists have advocated for menstrual status to be considered a “vital sign” at routine clinical visits, given the importance of estrogen for bone and other tissues (40). Many individuals with this disorder will provide a history of normal menarche and regular

menstrual cycles between 26 and 35 days in length. These women typically are intelligent, high-achievers, who are usually thin or of normal body weight. A detailed interview may identify a stressful event or emotional crisis (divorce, relation breakup, death of a friend or relative) preceding the amenorrhea. Other interpersonal and environmental stressors may also be present such as academic pressures, job stresses, or psychosexual problems. A careful review of the patient's current lifestyle including exercise intensity, dietary choices, and the use of sedatives or hypnotics may be helpful in characterizing the psychogenic stress components. The patient may have features of the female athlete triad, which consist of amenorrhea, insufficient caloric intake with or without an eating disorder, and low bone density or osteoporosis.

The physical examination should focus on identifying galactorrhea, thyroid dysfunction, and evidence of hyperandrogenemia (i.e., acne, hirsutism). The pelvic examination should be normal except for a thinned vaginal mucosa or absent cervical mucus which are characteristics of hypoestrogenism. Despite these findings, these patients do not usually experience hot flushes.

(Table 3, 4)

Laboratory evaluation should include FSH, prolactin (PRL), and TSH. Most of the other pituitary hormones should be in the normal range (Table 4). In many patients, the progestin challenge test (medroxyprogesterone acetate 10 mg for 7 days) will demonstrate an absence of withdrawal uterine bleeding or vaginal spotting. This test is a bioassay for the absence of estrogen priming of the endometrium and reflects the chronically low circulating levels of estradiol.

The basic defect in women with functional hypothalamic amenorrhea is the failure of the hypothalamus to increase GnRH output in the presence of severe hypoestrogenism. Most investigators believe that there is a slowing of the GnRH pulse generator as reflected by a decrease in peripheral pulsatile LH secretion in these women. The pattern of LH secretion may vary. During the early onset, LH pulse frequency and amplitude may be normal, and in more severe cases, regression to a prepubertal pattern may occur. During recovery from HA, sleep- associated increases may be observed (see Figure 1).

The pituitary gland is fully functional and capable of synthesizing and release of LH and FSH. However, responses to exogenous GnRH in these individuals may vary depending on the endogenous GnRH priming of the pituitary gland. LH and FSH responses to exogenous GnRH may be absent, normal, or supernormal. In these patients, after a period of priming with intravenous pulsatile GnRH (1-2 mg/90 minutes), normal levels of LH and FSH can be restored and responses to exogenous GnRH become normal. Taken together, these observations suggest that endogenous GnRH secretion is deficient and, gonadotropin secretion and ovarian function can be normalized with physiologic replacement of exogenous, pulsatile GnRH.

Magnetic resonance imaging (MRI) of the brain is not routinely needed in patients with

presumed hypothalamic amenorrhea (41). However, it is indicated in patients who have a history of severe or persistent headaches, persistent vomiting that is not self-induced, central hypothyroidism, hyperprolactinemia or galactorrhea, or a change in thirst, urination, or vision.

Figure 1

CLINICAL MANAGEMENT OF FUNCTIONAL HYPOTHALAMIC AMENORRHEA

The clinical evaluation of HA should focus on a carefully conducted history and physical examination that reviews life style variables and interpersonal relationships. Since this is a diagnosis of exclusion, significant organic diseases must be excluded (Table 1). In many patients, spontaneous recovery of menstrual function will take place following accommodation to environmental stressors or after modification of life style. Psychological counseling may also be appropriate for these individuals. Because of the functional nature of HA, an individualized and expectant management should be considered the initial approach. In those who remain amenorrheic, periodic evaluation of menstrual status every 4 to 6 months is prudent.

In the infertile patient with this diagnosis who fails to resume normal cycles, a trial of low dose clomiphene citrate (25-50 mg for 5 days) is appropriate. In these patients, higher doses of clomiphene may suppress the H-P axis due to the weak estrogenic properties of clomiphene in an already hypoestrogenic environment. For clomiphene failures, use of human menopausal gonadotropins as an alternative method is highly successful. If available, pulsatile administration of GnRH 5 mg/90 minutes intravenously using a modified insulin pump will successfully induce ovulation after a 13 to 14 day treatment period (42). This latter approach is associated with ovulation rates of greater than 90% with generation of a single dominant ovarian follicle and much lower rates of ovarian hyperstimulation. In these patients, corpus luteum support can be maintained with either GnRH or human chorionic gonadotropin 1500 units intramuscularly every three days for 4 doses.

For the woman who remains amenorrheic for more than 1 year, the long term risks of hypoestrogenism including reduced bone mineral density and osteoporosis become factors. In young women with persistent hypoestrogenism, the bone mass can decrease at a rate of 2-5% per year for the first three to five years. Dual energy X-ray absorptiometry (DEXA) is often necessary to convince patients to begin estrogen therapy. The minimal dose of estrogen necessary to conserve bone has been established in menopausal women. At least 0.3 mg of conjugated estrogen, 1 mg of micronized estradiol, or 0.025 mg of transdermal estrogen is necessary to protect against bone loss. Use of a progestin on a cyclic basis such as medroxyprogesterone acetate for 10 to 12 days each month is necessary to ensure regularly shedding of endometrium and prevent endometrial hyperplasia. Calcium and vitamin D supplements may also be taken; however, the primary therapy requires treatment of the underlying process. The use of bisphosphonates in reproductive-aged women should be carefully considered.

As previously discussed, Leptin plays a critical role in regulation of kisspeptin and in HA. A possible future treatment for HA may include leptin replacement as it has been shown to restore pulsatility of gonadotropin-releasing hormone and ovulation as well as full development of secondary sexual characteristics in females with hypogonadotropic hypogonadism (43). However, the effect of leptin therapy on bone health is unknown. Similarly possible future treatments options may include exogenous kisspeptin.

Table 2. Associated Neuroendocrine Abnormalities in Hypothalamic Amenorrhea.

Increased daytime cortisol secretion
Increased amplitude and duration of nocturnal melatonin secretion
Increased nocturnal secretion of GH
Elevated CRH levels in cerebral spinal fluid
Blunted elevation of PRL, ACTH, and cortisol during the noon meal

Table 3. Common Features of Women with Psychogenic Hypothalamic Amenorrhea

Single marital status
Obsessive-compulsive habits
History of significant stressful life events
History of sexual abuse
History of prior irregular menstrual cycles
Normal or thin habitus
Tendency to use sedatives or hypnotic drugs
Involved in professional occupations
High intelligence

Table 4. Expected Serum Hormonal Parameters in Functional Hypothalamic Amenorrhea

Hormone	**Expected Values**
LH	Normal or low
FSH	Normal or low
PRL	Normal or low
TSH	Normal
GH	Normal or low
Estradiol	Normal or low
ACTH	Normal
Cortisol	Daytime elevation with diurnal variation
Testosterone	Normal or low
T_3	Normal
T_4	Normal

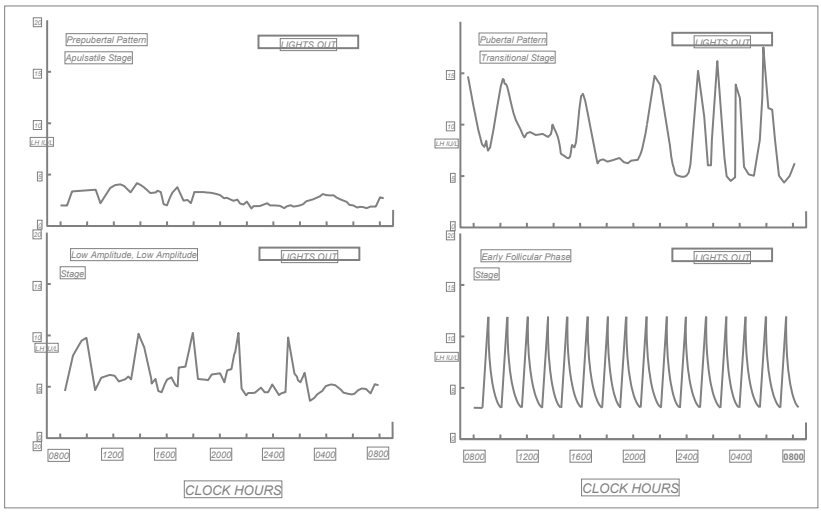

Figure 1. Examples of LH pulsatile secretion at various stages of the hypothalamic-pituitary activation. GnRH-LH secretion can progress from an apulsatile stage; to a high amplitude infrequent pulse stage; to a sleep-entrained pulse stage; and to regular every ninety minute pulse (1).

BULIMIA AND ANOREXIA NERVOSA

Severe eating disorders such as bulimia and anorexia nervosa are also associated with disruption of reproductive function. Bulimia is characterized by alternating episodes of consumption of large amounts of food over a short time (binge eating) followed by periods of self-induced vomiting, excessive use of laxatives or diuretics and food restriction. The incidence of bulimia is estimated to be 4.5 to 18 percent among high school and college students (44). Bulimia usually begins between the ages of 17 to 25 years.

Anorexia nervosa is a severe eating disorder characterized by extreme weight loss (greater than 25% of ideal body weight), body-image disturbance, and an intense fear of becoming obese (45). Anorexia patients are usually between the age of 12 yrs and the mid-thirties and have a bimodal age of onset at 13-14 years and 17-18 years. There is a 90 to 95 % female predominance with the majority of patients coming from Caucasian, middle-class or upper-middle class families. The overall incidence of anorexia ranges from 0.64 per 100,000 to 1.12 per 100,000. The mortality associated with anorexia has been reported to be as high as 9 percent usually secondary to cardiac arrhythmia which is precipitated by electrolyte abnormalities and/or diminished heart muscle mass. Suicide has also been more common (2 to 5%) in patients with anorexia nervosa. These statistics are sobering making it extremely important for the clinician to recognize

early signs of this disorder so that appropriate intervention and treatment can be initiated.

The clinical features of bulimia and anorexia are listed in Tables 5 and 6. Due to the marked reduction in caloric intake in anorexia, basal metabolism is lowered by decreased conversion of thyroxine to triiodothyroxine to maintain homeostasis. Thyroxine is converted via an alternative pathway to reverse triiodothyroxine, a relatively inactive isoform (Table 7). This protective functional mechanism is also commonly seen in severely ill patients and during prolonged starvation. Anorexics also suffer from defects in thermoregulation and are hypothermic. Because secretion of vasopressin is impaired, anorexics also have partial diabetes insipidus and are unable to concentrate their urine.

Anorectic and bulimic patients have hyperactivation of the HPA axis (46). Studies show a persistent hypersecretion of cortisol throughout the day with an increase in 24 hour free cortisol secretion. Despite the increased cortisol production, the manifestations of hypercortisolism are not present due to a decrease in cellular glucocorticoid receptors (47). The reduced number of these receptors may also provide an explanation for the incomplete suppression of the pituitary-adrenal axis by dexamethasone. Pituitary CRH responses are also blunted in bulimics and anorectics. As with other stress response syndromes, anorexics have evidence for increased central opioid activity with reported increases in cerebrospinal fluid levels of β-endorphins (48). Hypolepitinemia is commonly seen in women with anorexia. In these patients the low levels of leptin are representative of a chronic energy deficiency (49).

Like functional hypothalamic amenorrhea, anorexics have a prepubertal pattern of LH secretion presumably due to marked decrease in GnRH secretion. With weight gain, anorexics can display transitional patterns of LH secretion and may have normal or supranormal responses to GnRH (Figure 1). In some patients, despite return to normal body weight, up to 50% remain anovulatory.

Table 5. Common Features of Bulimia

Irregular menstrual cycles
Dental enamel erosion
Acute irritation of esophageal mucosa
Esophageal or gastric rupture
Hypokalemia
Aspiration pneumonia
Ipecac poisoning

Table 6. Common Features of Anorexia Nervosa

Preoccupation with handling of food
Bulimic behavior

Calorie counting Distortion of body self-image Hyperactivity Obsessive-compulsive personality Increased incidence of past sexual abuse
Amenorrhea Constipation Coarse, dry skin Soft, lanugo-type hair
Hypothermia with defective thermoregulation Mild bradycardia Cardiac arrhythmia Hypotension
Hypokalemia secondary to diuretic or laxative abuse Low bone mass Increased serum beta-carotene levels Anemia Leukopenia Elevated hepatic enzymes

Table 7 Neuroendocrine Abnormalities Associated with Anorexia Nervosa

Diminished GnRH-LH pulsatile frequency and amplitude Low blood LH and FSH levels Impaired ACTH response to CRH stimulation testing Resistance to dexamethasone suppression Increased ACTH levels Increased 24 hour urinary free cortisol levels Low prolactin levels Low TSH levels High reverse T_3 and low T_3 levels Elevated GH levels Decreased IGF-1 levels Diabetes insipidus

The success rates for treatment of anorexia nervosa and bulimia remain low. Therapeutic approaches include behavior modification, group therapy, and individual psychotherapy. Generally, a team approach consisting of a psychiatrist and a general medicine specialist with expertise in eating disorders is desirable. Because of the high mortality rate and the significant morbidity associated with anorexia, it is important to obtain psychiatric consultation and follow-up in all patients with eating disorders. For

patients who fail to resume menstrual function even after restoration of body weight, estrogen replacement therapy is indicated.

EXERCISE-INDUCED HYPOTHALAMIC AMENORRHEA

With the increased participation of women in all types of recreational and competitive athletic activities, health issues related to exercised-induced amenorrhea have become common. Depending on the type of sport and competition level, the incidence of amenorrhea varies from 5 to 25%. The incidence of menstrual irregularities appears to be greatest in sports that favor a low body weight physique such as ballet dancers (6-43%) and middle and long distance runners (24-26%). The incidence appears to be less frequent in bicyclers (12%) and swimmers (12%) (50).

In those athletes with menstrual irregularity, LH pulsatility is altered and can range from a decreased frequency to a transitional pattern (Figure 1). It is well known that acute exercise leads to hyperactivation of the HPA axis. Is it the stress of exercise or the low energy availability that alters LH pulsatility in exercising women? This key question has been answered in part by controlled studies in which women undergo dietary caloric restriction imposed in the face of increasing exercise demands. It would appear that LH pulsatility is not disrupted by the stress of exercise but rather LH pulsatility is disrupted because of reduced energy availability (51).

It is important to emphasize for so many of these athletes that the “female athlete triad” amenorrhea, osteoporosis, and eating disorders coexist. Management of these patients should emphasize measurement of bone density, counseling about diets, weight changes, trying to keep weight near normal levels, and calcium intakes. Women with exercise-related amenorrhea tend to have impaired lipid and metabolic profiles including an elevated serum total cholesterol, LDL cholesterol, and triglycerides compared with healthy women (52). One goal of therapy should be to decrease the level of exercise, improve the diet, and achieve weight gain. For others, exercise may not induce amenorrhea but may be associated with longer menstrual cycles, luteal phase defects, and intermenstrual spotting. These reproductive defects may be reversible with a decrease in exercise level or intensity. Alternatively, clomiphene given at doses between 25-100 mg for 5 days may increase GnRH pulsatility sufficiently to correct this defect. If amenorrhea persists for over 6 months, it may be prudent to begin estrogen replacement therapy or oral contraceptive pills. Long term health risks in these individuals are reproductive dysfunction and skeletal abnormalities.

OTHER CAUSES OF HYPOGONADOTROPINISM

Isolated Gonadotropin Deficiency (IGD)

This disorder is characterized by a decrease or absence of endogenous GnRH secretion resulting in very low to undetectable LH and FSH levels. Individuals with this disorder have incomplete development of secondary sexual characteristics, primary amenorrhea, eunuchoid features, and in some cases a decreased sense of smell or anosmia (Kallmann syndrome) (53). This disorder can have an autosomal dominant

inheritance pattern. IGD has been linked to variance in over 15 genes. Common genetic variants include KAL1, FGFR1, PROKR2, PROK2, CHD7, FGF8, KISS1, KISS1R, TAC3, TACR3, GNRHR, and GNRH1 (54). The underlying defect is due to a failure of GnRH neurons to form completely in the olfactory placode or to migrate from the olfactory bulb to the media basal hypothalamus during early embryo development. For individuals with anosmia or hypo-osmia, there is evidence of hypoplasia of the olfactory bulbs on magnetic resonance scan (55).

Baseline levels of LH and FSH may be in the prepubertal or normal range. However, levels of other pituitary hormones such as TSH, GH, PRL, and ACTH are normal. Due to the failure to increase gonadal sex steroid secretion during puberty, secondary sex characteristics fail to develop and closure of the epiphyseal plates of the long bones is delayed resulting in a eunuchoid habitus where the arm span is greater than the height.

In many cases individuals are started on birth control pills without the diagnosis being made, such that there is partial or complete development of secondary sexual characteristics. In the untreated patient, breast development is usually Tanner stage I or II while pubic hair development will be Tanner IV or V. Treatment of IGD will require estrogen therapy to induce progressive pubertal maturation (100 ng/kg/day of ethinyl estradiol). Patients should be monitored at 2 or 3 month intervals to determine the rate of skeletal growth and development. The addition of a progestin such as medroxyprogesterone acetate 10 mg/day for 12 days can then be used to shed the endometrium. Progesterone therapy should only be started after optimal breast development is achieved. Once sexual maturation is completed, the estrogen dose can be gradually increased and maintained on 2 mg of micronized estradiol or 0.625 mg to 1.25 mg of conjugated estrogens with 12 days of progestin each month. When fertility is desired, ovulation induction can be carried out with either human menopausal gonadotropins or pulsatile GnRH administration.

Postpartum Pituitary Necrosis (Sheehan Syndrome)

Postpartum pituitary necrosis is usually preceded by a history of severe obstetrical hemorrhage with hypotension, circulatory collapse, and shock. After fluid resuscitation of the patient, this condition may be manifested by clinical evidence of partial or panhypopituitarism. Simmonds was the first to describe this clinical syndrome although the most complete description has been attributed to Sheehan (56). This condition constitutes an endocrine emergency that can be life-threatening.

The pathophysiology of this process is not entirely clear. With pregnancy, there is an increase in blood supply to the pituitary bed and the pituitary gland enlarges. During the period of profound hypotension, Sheehan postulated that occlusive spasm of the arteries that supply the pituitary and stalk occurs. This leads to venous stasis and thrombosis of the pituitary portal vessels causing a variable degree of pituitary ischemia and cell death. Many patients initially present with a failure to have breast engorgement and lactation due to a deficiency in PRL secretion. These women may also have other anterior pituitary deficiencies. The posterior pituitary is usually spared because it is less dependent on the portal blood supply. In some patients, the absence of ACTH

secretion leads to inadequate cortisol secretion resulting in postural hypotension, nausea, vomiting, and lethargy. Hypothyroidism may be noted later in this scenario. However, in the majority of women, there is a diagnostic delay due to the vague symptoms. Recovery of pituitary function has been reported in a few cases.

The extent of pituitary deficiencies can be characterized by provocative testing with a combined intravenous injection of the hypothalamic releasing factors GnRH, TRH, GHRH, and CRH (57). Appropriate replacement therapy can be instituted once the pituitary reserve is defined. For the patient who presents with hypotension, immediate administration of glucocorticoids is required (cortisone acetate 100 mg, IM). Once the patient stabilizes, a maintenance dose of cortisone acetate 20-25 mg/day or prednisone 5 mg/day can be given. With increased stressful conditions such as an infection, a doubling or tripling of daily doses should be used. For hypothyroid patients, thyroxine replacement should be replaced gradually beginning at 50 μg/day and increased at 50 μg increments at 1 week intervals until full replacement doses are reached (0.1 to 0.2 mg/day). Patients should be instructed to wear a medical alert bracelet. Estrogen replacement therapy will be required for persistent amenorrheic patients. If fertility is desired, ovulation induction with exogenous gonadotropins is required.

Post-traumatic Hypopituitarism

This condition can arise following severe head trauma as a result of a sudden deceleration of the head and occult damage to the pituitary stalk or hypothalamus during a traffic accident (58). Trauma may also be associated with a basal skull fracture or an episode of unconsciousness. The risk for post-traumatic hypopituitarism is generally higher after a severe brain injury requiring neurosurgical interventions than for a mild or moderate injury (59). These individuals will often manifest a delay from injury to presentation of up to 10 years post-injury, possibly due to ongoing atrophy of the sellar and perisellar structures. The symptoms range from partial to complete panhypopituitarism. These symptoms can include amenorrhea, galactorrhea, hypogonadism, loss of axillary and pubic hair, anorexia, and weight loss. For these patients, evaluation of the pituitary-adrenal axis is most important because hypocortisolism can be potentially life-threatening. The diagnostic evaluation and management is similar to that described for Sheehan syndrome.

Pituitary Apoplexy

This medical emergency is characterized by an acute infarction of the pituitary gland. Patients will complain of a sudden onset of a severe retro-orbital headache and visual disturbances which may be accompanied by lethargy or loss of consciousness (60). These symptoms may mimic other neurological emergencies such as hypertensive encephalopathy, cavernous sinus thrombosis, ruptured aneurysm, or basilar artery occlusion. CT or MRI imaging may indicate hemorrhagic changes in the pituitary sella region. Patients with pituitary tumors are at higher risk for this complication. For some patients, neurosurgical consultation and emergency decompression may become necessary. Provocative testing as describe for Sheehan syndrome should be performed to evaluate for multiple pituitary deficits. Appropriate replacement of target tissue hormones should be instituted based on testing.

Post radiation-Induced Hypopituitarism

Exposure to therapeutic radiation sources for treatment of midline CNS tumors can place patients at increased risk for delayed development of hypopituitarism (61). In general, sensitivity to radiation is greatest for somatrotropes and gonadotropes, followed by corticotropes and thyrotropes. The onset of pituitary deficiencies may be insidious but can occur within 1 year of radiotherapy. Periodic assessment of hypothalamic-pituitary function should be performed for an indefinite period of time and appropriate replacement hormone therapy should be instituted as these deficiencies develop.

SUMMARY

In this chapter, we have reviewed a variety of disorders that can disrupt the normal menstrual cycle. Whether the disorder is linked to central organic lesions, changes in life style, or functional, stress components, all appear to have a common pathway(s) resulting in alterations in the secretion of the GnRH pulse generator.

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