Stress, Emotional Eating, and Reproductive Function

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LEARNING OBJECTIVES

At the conclusion of this presentation, participants should be able to:

- Delineate the role of stress as a cause of functional hypothalamic amenorrhea and emotional eating
- Recognize the clinical manifestations of disordered eating
- Understand the mechanisms by which energy imbalance sensitizes the reproductive axis to psychogenic stressors
- Consider the treatment implications of the link between stress, metabolism, and reproductive function
- Highlight the role of cognitive behavior therapy (CBT) in the treatment of functional hypothalamic amenorrhea (FHA) / stress-induced anovulation / amenorrhea (SIA) and emotional / disordered eating
Disclosures

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Menopause, Editorial Board, 1999-present
The Endocrine Society
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Reproductive outcomes linked to (maternal) weight and stress

- Anovulation
- Infertility
- Miscarriage
- Preterm labor
- Pre-eclampsia
- Gestational diabetes
- Fetal macrosomia
- Intrauterine growth restriction
- Congenital anomalies
- Fetal origins of adult disease
What is the difference between eating disorders, disordered eating, and emotional eating?

- DSM (Diagnostic and Statistical Manual) produced by the APA (American Psychiatric Association) defines the criteria for eating disorders
- Disordered eating is when food intake does not correlate with energy demands and includes eating too much or too little and/or insufficient/inappropriate nutrient content
- Emotional eating has been defined as the propensity to eat in response to negative emotions and has been linked to stress
- Emotional eating includes alterations in food preferences as well as eating more or less or at atypical times (nocturnal eating)
What is the difference between eating disorders, emotional eating, and disordered eating?

- DSM defines eating disorders as a persistent disturbance of eating that impairs health or psychosocial functioning
  - anorexia nervosa
  - avoidant/restrictive food intake disorder
  - binge eating disorder
  - bulimia nervosa
  - pica
  - rumination disorder
  - atypical
  - unspecified (NOS = Not Otherwise Specified)

- Significant co-morbidities include DSM diagnosable depression, anxiety, obsessive-compulsive disorder, alcohol and other drug use / abuse
What is the difference between eating disorders, disordered eating, emotional eating, FHA, and obesity?

- The diagnosis of an eating disorder (ED) is typically rendered by a psychiatrist or psychologist
- Disordered eating is a less specific term and refers to less typical ingestive patterns
- Emotional eating recognizes that food is hedonic and its ingestion may reduce stress
- Functional hypothalamic amenorrhea is a gynecologic diagnosis
- Emotional eating predisposes to obesity and also impacts reproductive outcomes
- Stress-induced obesity masquerades as PCOS
Eating disorders and reproductive outcomes

- **Increased risk of**
  - infertility (OR 1.9)
  - fertility treatments (OR 1.9)
  - twin births
  - unplanned pregnancy
  - miscarriage

- **Unlikely to be recognized by infertility specialists**
  - Micali et al. BJOG 2012;119:1493
  - Micali et al. BJOG 2014;121:408
  - Bye A et al. BMC Pregnancy Childbirth 2018;18:114
Functional hypothalamic amenorrhea

- Not defined as an eating disorder in the DSM
- May be due to a combination of psychological stressors and metabolic imbalance, including undernutrition and overnutrition
- Classically linked to undernutrition and altered body image but does not meet formal DSM criteria for an ED
- Ascribed in part to cognitions that spur disordered eating
- Often associated with high energy expenditure and/or insufficient energy intake to meet demand (athleticism)
- Can occur in the absence of energy imbalance
Obesity

- May be viewed as an eating disorder but is not defined as such by DSM
- Linked to emotional and disordered eating
- Ascribed to the interaction of psychological stressors, including food insecurity, and the availability of low nutrient foods
The predicted probability of conception with body mass index (BMI kg/m²), after adjusting for age, smoking, race, education, occupation.

Fertility is readily compromised by being “too thin.”

The predicted probability of conception with body mass index (BMI kg/m²), after adjusting for age, smoking, race, education, occupation

Fertility is relatively preserved despite high BMI

Weight and reproduction

- Underweight more than overweight is associated with anovulation and infertility

- Overweight more than underweight is associated with poor obstetrical outcomes
Energetics and metabolism of human reproduction

Pregnancy
- BMR ↑ 4% in 1st T, 10% in 2nd T, 24% in 3rd T
- Energy requirements ↑ 0 in 1st, 350 kcal/d in 2nd T, 500 kcal/d in 3rd T
- Mean TEE in pregnant women 11.5 vs 9.9 MJ/24 h
- Part of energy cost offset by reduction in physical activity

Labor and Delivery

Lactation
- If exclusive, 2.6 MJ/day

Human offspring cost a great deal to raise
- Human infants virtually always held by someone
- Once weaned, children must be provisioned with food
- Most foragers > 19 y before they produce more than they consume
- It takes **13 million calories** to raise a human from birth to maturity

Wadi Rum, extension of The Great Rift Valley from Ethiopia into Jordan, home to some of the earliest humans.

Human evolution required metabolic adaptation to low fuel environments and food insecurity was normative.

Nutrition transition: 2000 first time that overnutrition = undernutrition globally but food insecurity remains a concern.
How fares weight homeostasis?

- Excess body weight is the 6\textsuperscript{th} most important risk factor for global disease burden
  - Primarily due to ↓ physical activity + passive overconsumption of energy dense foods
  - Reflects gene x environment interaction with ↑ risk of obesity greatest in disadvantaged populations

- Consequences
  - Metabolic syndrome
  - CVD
  - Diabetes
  - ↓ Life expectancy
  - Reproductive compromise

Health Consequences of Chronic Stress

Chronic exposure to socio-environmental stressors

- Unrelenting
- Unpredictable
- Unresolvable

Neurobehavioral response

- Dysregulation of LHPA axis
- Chronic activation of SNS
- Behavioral Coping (adaptive or maladaptive)

Increased health burden / disorders / disease susceptibility / aging

- Affective disorders
- Reward deficits
- Disordered eating
- Reproductive compromise
- Bone loss
- CVD and stroke
- Immune dysfunction
The neuroendocrine signature of stress

• Increased CRH drive and secondary hypercortisolism
• Decreased TRH input and secondary hypothyroidism (sick euthyroid syndrome)
• Suppression of GnRH drive with secondary anovulation and hypoestrogenism

• Altered appetite signal release and pattern and altered responses to appetite signals
  • Weight gain or loss depending on circumstances

• Metabolic syndrome and associated consequences independent of weight
• Accelerated aging with shortening of telomeres
Subordination is a social stress that impairs reproduction AND alters appetite in nonhuman primates.
Ovarian Function In Dominant vs Subordinate Monkeys

Dominant
- Normal: 88%
- Anovulation: 3%
- Luteal insufficiency: 9%

Subordinate
- Normal: 54%
- Luteal insufficiency: 23%
- Anovulation: 23%
Social Status, Food Intake, and Diet Preference

Diet choice, cortisol reactivity, and emotional feeding in socially housed rhesus monkeys
Physiology & Behavior 2010;101:446-455.
39 ovx adult female rhesus monkeys living in social groups randomized to **Low Fat, High Fiber Diet (LCD)** or **choice of LCD and High Fat, High Sugar Diet (HFSD)**

- All monkeys preferred HFSD to LCD
- Subordinate monkeys ate more when given a choice of LCD or HFSD whereas dominants ate the same during LCD and HFSD choice
- Insulin and glucose were higher with HFSD even when caloric intake did not increase
- **Cortisol levels were higher during the social stress of separation when monkeys were given HFSD choice**
- Subordinates demonstrated reduced glucocorticoid negative feedback
- **Higher cortisol after dex suppression predicted HFSD intake but not LCD intake**
- The cortisol response to social stress of separation predicted intake of HFSD in all independent of social rank

Michopoulos V et al. Psychoneuroendocrinology 2012
Antagonism of corticotrophin-releasing factor type 1 receptors with Antalarmin attenuated caloric intake of free feeding subordinate female rhesus monkeys in a rich dietary environment

Kcal consumed across the 2-day placebo and Antalarmin conditions for dominant and subordinate females.

White reflects intake of the laboratory chow diet (LCD) and black reflects intake of the calorically dense diet (CDD).

The P-value reflects significant treatment by status interaction.

GABA-A receptor binding in limbic regions implicated in emotional processing before and after CRH antagonism in dominant (D) and subordinated (S) monkeys.

CRH receptor antagonism (astressin B) reversed the differential impact of social subordination upon central GABA-A receptor binding in prefrontal cortex.

Additional observations

- Women with anorexia nervosa are insensitive to ghrelin infusions
  - Miljec et al JCEM 2006
- Slowing of LH pulses by ghrelin in monkeys reversed by CRH antagonist astressin
  - Vulliemoz et al 2008
  - Berga editorial Endocrinology 2008
Metabolic influences on neuroendocrine regulation of reproduction

Schematic representation of neural interactions between metabolic and reproductive functions depicting likely sites of action of leptin, insulin, and ghrelin to control GnRH release. 3V, third ventricle; ARC, arcuate nucleus; ME, median eminence; PMV, ventral premammillary nucleus; POA, preoptic area.

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Schematic representation of neural interactions between metabolic and reproductive functions depicting likely sites of action of leptin, insulin, and ghrelin to control GnRH release. 3V, third ventricle; ARC, arcuate nucleus; ME, median eminence; PMV, ventral premammillary nucleus; POA, preoptic area.

Stress, emotional eating, weight, and reproduction

- Both undernutrition / low weight and overnutrition / obesity compromise reproductive function
  - Different states elicit a different constellation of endocrine and epigenetic changes
  - Different - but nonetheless - deleterious maternal and fetal impact

- Social stress may elicit undernutrition or overnutrition
  - Overnutrition is more common when energy dense food is readily available
  - Eating may moderate the endocrine response to stressors
  - Food choice may increase stress
  - Obesity may be an easily recognized marker of stress
Food for thought

Not all overweight women have PCOS

Obesity may reflect stress-induced overeating

Certain nutrients amplify stress and increase cortisol, glucose, and insulin whereas other nutrients blunt stress sensitivity
Will stress management that reduces cortisol levels foster eating behaviors that result in weight loss in women who are obese?
Treatment Considerations

Can we develop stress management strategies for women with stress-related obesity and reproductive compromise by extrapolating from treatments for women who have stress-induced anovulation?
Which one of these fertility statuettes is most likely to have stress-induced anovulation?
FHA is more than infertility due to anovulation
FHA is a diagnosis of exclusion

- **Hypothalamic**
  - Isolated GnRH deficiency (± anosmia)
  - Tumors
  - Head trauma (stalk transection)
  - Drugs (neuroleptics, opiates)
  - Functional / behavioral (pseudocyesis, eating disorders, medical conditions, exercise, depression, stress, etc)

- **Pituitary**
  - Adenomas, tumors
  - Postpartum pituitary apoplexy
  - Hypopituitarism

- **Thyroid**

- **Adrenal**
  - Cushing’s, Addison’s
  - CAH, tumors

- **Ovarian**
  - Gonadal dysgenesis, POI
  - PCOS, tumors

- **Uterine**
  - Agenesis
  - Asherman’s
  - Androgen Insensitivity Syndrome (T Fem)
  - 5α-reductase deficiency

- **Cervical**

- **Vaginal**
The designation “functional” hypothalamic amenorrhea implies absence of “organic” causes and the potential for recovery if the behavioral concomitants are ameliorated.

**Functional** hypothalamic hypogonadism / stress-induced anovulation / *many names*

- Spectrum of menstrual cycle compromise due to variably reduced GnRH drive
- Concomitant hypothalamic hypercortisolism
- Concomitant hypothalamic hypothyroidism
- Other neuroendocrine alterations
- **Synergism between energetic imbalance and psychogenic challenge**

Berga SL et al. Constellation of neuroendocrine aberrations in FHA. JCEM 1989
The H-P-O Axis

Hypothalamus

Pituitary

Ovary or Testes

GnRH

LH FSH

CNS influences including stress

Steroidal and Nonsteroidal Feedback
How does stress compromise reproductive function?

Metabolic x psychogenic stressors induce a constellation of neuroendocrine adaptations:

- Suppressed GnRH lowers LH/FSH drive
- Suppressed TRH-TSH drive lowers T3 and T4
- Activated CRH-ACTH drive elevates circulating and central cortisol

Proximate cause of suppressed ovarian function (anovulation) is ↓GnRH manifested by ↓LH pulse frequency

The active signal – free cortisol – was higher in CSF than circulation because 1) CBG in circulation binds cortisol and reduces free fraction and 2) decreased clearance from CSF relative to circulation.
Pathogenesis of FHA / SIA: hypothalamic hypothyroidism facilitates energy conservation and weight stabilization or gain at the expense of tissue and organ repair.

Berga SL et al Fertil Steril 1997
Figure 11-16. The spectrum of thyroid hormone concentrations in ill individuals. The most common pattern is reduction in serum $T_3$ concentration and elevation in serum $rT_3$ concentration. Although the total $T_4$ level may fall, the free $T_4$ level is generally normal except in seriously ill patients, especially if they are receiving glucocorticoids or dopamine. Serum TSH concentration generally remains in the normal range but may be suppressed in the very sick patient or by dopamine or glucocorticoids. In some patients, particularly during the recovery phase, the TSH level transiently rises above normal in patients who have no evidence of permanent thyroid dysfunction. (From Brent GA, Hershman JM. Effects of nonthyroidal illness on thyroid function tests. In: Van Middlesworth L, ed. The Thyroid Gland: A Practical Clinical Treatise. Chicago: Year Book Medical, 1986: 83–110.)
Evidence of allostasis (chronic stress) in FHA

HPO insensitive to ↓ ovarian sex steroid secretion (↑ feedback sensitivity to E2)
  • FSH not elevated and no hot flashes despite reduced E2
  • Feedback sensitivity to E2 increased akin to prepuberty
  • Energy conservation

HPA axis displays altered feedback inhibition
  • Despite ↑ cortisol, CSF CRH comparable indicating ↓ feedback sensitivity
  • Altered metabolism

HPT - hypothalamic hypothyroidism / sick euthyroid syndrome
  • ↓ T3 and ↓ T4 without a compensatory rise in TSH
  • Energy conservation
  • Not readily reversed with exogenous T4 replacement
  • May compromise fetal brain development if not reversed

Stress alters feedback sensitivity to appetite signals
  • High stress reduces appetite and favors anorexigenic signal responsivity
  • High stress + high fat, high sugar “fuel” availability favors emotional eating
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Pathogenesis of functional hypothalamic amenorrhea / stress-induced anovulation

**METABOLIC IMBALANCE**

energy expenditure ≠ energy intake

**PSYCHOGENIC CHALLENGE**

↓H-P-Ovary

↑H-P-Adrenal

↓H-P-Thyroid

To eat or not?
Synergism between metabolic and psychosocial stress in monkeys

- All monkeys received a mild social stress (move to a novel room)

- Before the social stress, 50% of monkeys given a metabolic challenge of 20% calorie restriction + running 2-3 mi/d

- Reproductive function followed longitudinally with serial estradiol & progesterone

Williams, Berga, Cameron. Am J Physiol Endo Metab 2007
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*Williams, Berga, Cameron. Am J Physiol Endo Metab 2007*
Exercise-induced decline in glucose only in FHA

Despite comparable BMI, FHA did not meet energetic demands of sub-maximal expenditure

Exercise resulted in greater HPA (adrenal) activation in FHA vs eumenorrheic women (EW)

State dependent response to metabolic challenge likely due to pre-existing HPA activation

Amplified cortisol response to exercise challenge in FHA vs eumenorrheic women (EW) likely elicited by drop in glucose

Sanders et al. AJOG 2018

**Glucose**

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**Cortisol**

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Sanders et al. AJOG 2018
Heightened cortisol response to exercise challenge in women with FHA

Exercise initiation  Exercise termination

Glucose (mg/dL) vs Time (min)

- EW
- FHA

Sanders, Kawwass, Loucks, Berga. AJOG 2018;218:230.e1-230.e6
Misaligned cognitions → \( \uparrow \text{CRH / Cortisol} \) → \( \uparrow \text{GABA} \) → Appetite & energy balance ↓GnRH drive → Energy imbalance

- 5HT
- E2
- Androgens
- Progesterone, Progestins

- Adiponectin, Leptin, etc
- Glucose, Insulin, ghrelin

Kisspeptins
Aligned cognitions \rightarrow \downarrow CRH / Cortisol \rightarrow \downarrow GABA

\rightarrow 5HT, E2, Androgens, Progesterone, Progestins

\rightarrow \downarrow GABA

\rightarrow \downarrow CRH / Cortisol

\rightarrow Adiponectin, Leptin, etc

\rightarrow Kisspeptins

\rightarrow Appetite & energy balance

\rightarrow \uparrow GnRH drive

Energy balance
Cognitions drive behaviors
and both together alter neuroendocrine secretory patterns
Psychometric inventories in EW vs FHA/SIA

- BDI
- HAM-D
- DAS
- EDI-DT
- EDI-IE
- BULIT
- BMI

- Perfectionism
- High need for social approval
- External locus of control

Marcus MD et al. Fertil Steril 2001;76:310
Psychological profile of women with FHA / SIA: attitudes that heighten stress sensitivity

- Unrealistic expectations of self and others
- Perfectionism + high need for social approval (conflicting aims)
- Poor problem-solving and coping skills
- No excess history of negative life events
- Do not meet DSM criteria for depression, other psychiatric conditions, eating disorders

Aim of CBT was to change attitudes and restore internal locus of control rather than prescribe behavior change

16 sessions, 45 min each, over 20 weeks focused on:

- What is good nutrition and enough exercise (did not urge weight gain or change)
- Problem-solving strategies and coping mechanisms
- Developing realistic attitudes and expectations
- Best ways to deal with specific and common stressors

Berga SL et al Fertil Steril 2003;80:976
CBT reduced cortisol in the overnight sleep phase
CBT reduced circulating cortisol in FHA/SIA
Leptin and TSH increased following CBT

- **BMI**: Observed an increase following CBT.
- **Leptin**: Significant increase post-CBT compared to pre-CBT.
- **TSH**: Statistically significant increase post-CBT.
- **freeT3**: No significant change observed.

Graphs showing changes in BMI, Leptin, TSH, and freeT3 levels before and after CBT treatment.
Cognitive Behavior Therapy / Stress Management

- Lowers cortisol and restores reproductive function
- Improves metabolic variables
- Restores autonomy and sense of social control
- Effect size accrues indefinitely
- May mitigate the impact of poor socioeconomic circumstances (social determinants of health)
- Has the potential to improve maternal and child health independent of weight change
- Has the potential to modify appetite and food preference
- May be initiated concomitantly with other interventions
Functional Hypothalamic Amenorrhea: An Endocrine Society Clinical Practice Guideline

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Cosponsoring Associations: The American Society for Reproductive Medicine, the European Society of Endocrinology, and the Pediatric Endocrine Society. This guideline was funded by the Endocrine Society.
Treatment of FHA and Concomitant Medical Conditions: Estrogen Administration

3.4 We suggest against the use of OCPs in patients with FHA for the sole purpose of regaining menses or improving BMD. (2|⊕⊕○○)

3.5 In patients with FHA using OCPs for contraception, we suggest educating patients regarding the fact that OCPs may mask the return of spontaneous menses and that bone loss may continue, particularly if patients maintain an energy deficit. (2|⊕⊕○○)

3.6 We suggest short-term use of transdermal E2 therapy with cyclic oral progestin (not oral contraceptives or ethinyl E2) in adolescents and women who have not had return of menses after 6–12 months of a reasonable trial of nutritional, psychological and exercise intervention. (2|⊕○○○)
3.9 In patients with FHA wishing to conceive, after a complete fertility work-up, we suggest:

- Treatment with pulsatile gonadotropin-releasing hormone (GnRH) as a first line, followed by gonadotropin therapy and induction of ovulation when GnRH is not available (2|⊕〇〇〇〇);
- Cautious use of gonadotropin therapy (2|⊕〇〇〇〇);
- A trial of treatment with clomiphene citrate for ovulation induction if a woman has a sufficient endogenous estrogen level (2|⊕〇〇〇〇);
- Against the use of kisspeptin and leptin for treating infertility (2|⊕〇〇〇〇);
- Given that there is only a single, small study suggesting efficacy, but minimal potential for harm, clinicians can consider a trial of CBT in women with FHA who wish to conceive, as this treatment has the potential to restore ovulatory cycles and fertility without the need for medical intervention. (2|⊕⊕〇〇〇〇)
FHA and ED synopsis

- Reproduction is metabolically expensive and energy dependent
- Therefore metabolism and reproduction are tightly aligned
- Stress alters metabolism including energy expenditure and ingestive behaviors
- Energy imbalance per se is a stressor
- The hallmark of chronic stress is activation of the limbic-hypothalamic-pituitary-adrenal axis
- Stress causes more that LHPA activation and suppression of GnRH drive
- Chronic hypercortisolism predisposes to metabolic syndrome
- Chronic stress has profound acute and chronic health consequences for individuals and their offspring
- Cognitive management of stress ameliorates associated neuroendocrine alterations
- FHA, ED, and some types of obesity are manifestations of stress
How do you decide when to offer what therapies to whom?

- Is there a BMI below or above which ovulation induction or IVF is unsafe?
  - Unsafe for whom?
- What if the patient appears unable or unwilling to weigh risks and benefits?
  - When is a psychiatric consult preferred versus required?
- When is it appropriate to deny care such as ovulation induction or IVF?
  - Who do you engage when you are uncertain or uncomfortable?
The evolving story of stress and infertility

● Preconception paternal stress exposure
  • Changes in epigenetic marks in sperm with reprogramming of DNA methylation, histone post-translational modifications, and small noncoding RNAs
  • MicroRNAs are attached to the outside of the sperm in the epididymis reflect stress sensitivity of the father
  • Stressed fathers have offspring who are less stress-sensitive (more stress resilient) regardless of the sex of the offspring

● Maternal stress during pregnancy
  • Intergenerational transmission of stress via changes in placental biology involving inflammatory, nutrient, and epigenetic pathways
  • What about gametes?

Morgan & Bale. Parental advisory: maternal and paternal stress can impact offspring neurodevelopment. Biol Psychiatry 2017
A generation game. The Economist Feb 24 2018
Dietary Sugar and Oocyte Health

- **Increased dietary sugar** in healthy female primates **inhibited oocyte maturation** and **early embryo gene expression** even though the oocytes were removed and fertilization and embryo growth occurred under euglycemic conditions.

- Those oocytes that fertilized showed **>1100 changes in blastocyst gene expression**.

Chaffin et al. Endocrinology 2014
Sex differences in reproductive health

- Stress can cause infertility in women and men
- Stressors are sex specific
- The endocrine, molecular, and epigenetic “signature” of stressors is sex specific
- The sex of the fetus and placenta modifies the impact of stressors during pregnancy
CONCLUSION

We have great opportunity to improve reproductive health

We can improve reproductive and thereby population health by:

• Mitigating social determinants of poor parental health
• Combining behavioral, pharmacological, and societal strategies to constrain stressors and their biological impact
• Translating knowledge about social determinants of health into therapeutic medical and social approaches
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