Stress, Addiction, and Reproductive Function

Sarah L Berga MD
Professor of Obstetrics and Gynecology and Psychiatry
Director, Division of Reproductive Endocrinology and Infertility
University of Utah School of Medicine
Salt Lake City, Utah, USA
DISCLOSURES – Sarah L. Berga, MD

CONSULTING:
- AMAG Pharmaceuticals, Inc. Advisory Board Meeting: November 10, 2017, Dallas, TX
- Lupin Women’s Health Advisory Board, September 23, 2018, Dallas, TX
- Ava AG Advisory Meeting, February 27, 2019, Chicago, IL

EDITORIAL BOARDS & POSITIONS:
- *Human Reproduction Update*, Associate Editor: 2017-present
- *International Society for Gynecological Endocrinology*, Executive Committee Member: 2004-present
- *Journal of Clinical Endocrinology and Metabolism*, Editorial Board: 2013-present
- *Menopause*, Editorial Board: 1999-present
- *UpToDate*, Peer Review Board: 2005-present
LEARNING OBJECTIVES

• Are stress, food addiction, and substance use mechanistically linked?
• How do the above behaviors individually and collectively impact reproductive function?
• Delineate core concepts in the neuromodulation of the hypothalamic-pituitary-ovarian axis
• Highlight the role of cognitive behavior therapy (CBT) in management of functional hypothalamic amenorrhea (FHA) / stress-induced anovulation (SIA) as a potential paradigm for treating food and substance addiction
Maternal stress linked to poor reproductive outcomes and a behavioral repertoire that includes environmental exposures and maladaptive coping mechanisms including altered food intake and substance use and abuse

- Anovulation
- Infertility
- Miscarriage
- Preterm labor
- Pre-eclampsia
- Gestational diabetes
- Fetal macrosomia
- Intrauterine growth restriction
- Congenital anomalies
- Fetal origins of adult disease
Addiction and substance use and abuse cluster and interact with other stressors = EXPOSOME

• Poverty
• Violence
• Psychosocial stress and distress
• External locus of control
• Reduced access to resources including health care and education
• Undernutrition and overnutrition
• Poor quality food
• Poor housing / no housing / troubled neighborhoods
• Sex / gender / economic disparities
• Social instability
Social determinants of premature death

- Behavior: 40%
- Genetics: 30%
- Social: 15%
- Healthcare: 10%
- Environment: 5%

WHO 2008 Report: Closing the Gap in a Generation
What is the difference between eating disorders, disordered eating, and emotional eating?

- **DSM** (American Psychiatric Association) defines 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).
- **Emotional eating** may be defined as food phobias or food addictions.
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 substance 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 that has been linked to behaviors.
- 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, exercise, and achievement
- 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
- **Food addiction / comfort food**
- Linked to emotional and disordered eating
- Ascribed to the interaction of psychological stressors, including food insecurity, and the availability of low nutrient foods
Food addiction and substance addiction in women: common clinical characteristics

- Study of 229 women seen in ambulatory settings in a public hospital (Grady Memorial Hospital in Atlanta GA)
- Food addiction diagnosed using Yale Food Addiction Scale which is based on DSM-IV criteria for substance use disorder (SUD)
- Women with food addiction and SUD were more depressed and had more PTSD symptoms compared to those without either
- Food addiction prevalence 18%
- SUD prevalence 31%
- Both had higher emotional dysregulation and higher levels of childhood and adult trauma

Hardy et al. Appetite 120:367-373, 2018
Weight, stress, addiction, and reproduction function

- Underweight more than overweight is associated with anovulation and infertility

- Overweight more than underweight is associated with poor obstetrical outcomes

- Weight is often a readily measured surrogate marker for stress and addictive behaviors including food and substance abuse that are initiated to manage stress and sustained by ongoing stress
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

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
- Substance use
- Disordered eating
- Reproductive compromise
- Bone loss
- CVD and stroke
- Immune dysfunction
Exposome modifies the H-P-O

CNS influences including stress

Hypothalamus

Pituitary

LH FSH

GnRH

Steroidal and Nonsteroidal Feedback

Ovary or Testes
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
How does stress compromise reproductive function?

Interaction of metabolic x psychogenic stressors induces a constellation of neuroendocrine adaptations:

- Suppressed GnRH lowers LH/FSH drive and causes anovulation and infertility
- Suppressed TRH-TSH lowers T3/T4 and causes “sick euthyroid syndrome”
- Increased CRH-ACTH drive increases cortisol and causes metabolic syndrome

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

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%
- Anovulation: 23%
- Luteal insufficiency: 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.
Stress and Emotional Feeding

- 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 (metabolic syndrome)
- 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
Blocking stress with a CRH antagonist reverses emotional eating

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.

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.
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.

Understanding the brain-gut axis
Peripheral signals of energy state (green boxes) impact hypothalamic centers of homeostatic control and alter CNS (brainstem and mesolimbic) function
Ghrelin, an orexigenic hormone secreted by the stomach, modulates appetite, eating, stress, substance use and reproductive function!


- **Ghrelin**, a 28 aa orexigenic hormone produced by the stomach and known to increase food reward behavior, also increases impulsivity. Anderberg RH. Neuropsychopharmacology 41:1199, 2016

- **Exogenous ghrelin administration increases alcohol self-administration** and modulates brain functional activity in heavy-drinking alcohol-dependent individuals. Farokhnia M. Molecular Psychiatry 23:2029, 2018

- **Ghrelin receptor (GHS-R1A) antagonism suppresses alcohol consumption** and the alcohol deprivation effect in rats following alcohol consumption. Suchankova P. PLoS ONE 8: e71284, 2013.
Ghrelin also links stress and reproductive compromise associated with undernutrition

- 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 Endocrinology 2008
  - Berga editorial Endocrinology 2008
- State-specific actions of ghrelin?
- Sex-specific actions of ghrelin?
Can we develop stress management strategies for women with substance use and abuse and stress-related obesity and secondary reproductive compromise by extrapolating from treatment paradigms used to reverse anovulation in women with functional hypothalamic amenorrhea (FHA) / stress-induced anovulation (SIA)?

Would CRH or ghrelin antagonists help to overcome substance use and abuse?

What is the likelihood of neuroplasticity (adaptation)?
Synergism between metabolic and psychosocial stressors 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
Synergism between metabolic and psychosocial stressors 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
Amplified cortisol response to exercise challenge in FHA vs eumenorrheic women (EW) likely elicited by drop in glucose

- 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

Sanders et al. AJOG 2018

### Glucose

<table>
<thead>
<tr>
<th></th>
<th>EW Before</th>
<th>EW After</th>
<th>FHA Before</th>
<th>FHA After</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mg/dL</td>
<td></td>
<td></td>
<td>80</td>
<td>70</td>
</tr>
</tbody>
</table>

### Cortisol

<table>
<thead>
<tr>
<th></th>
<th>EW Before</th>
<th>EW After</th>
<th>FHA Before</th>
<th>FHA After</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortisol</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ng/mL</td>
<td></td>
<td></td>
<td>50</td>
<td>70</td>
</tr>
</tbody>
</table>
Heightened cortisol response to exercise challenge in women with FHA

Exercise initiation  Exercise termination

Glucose (mg/dL)

Time (min)

EW
FHA

Sanders, Kawwass, Loucks, Berga. AJOG 2018;218:230.e1-230.e6
Misaligned cognitions \(\rightarrow\) \(\uparrow\) CRH / Cortisol \(\rightarrow\) Energy imbalance

\(\uparrow\) GABA

5HT, E2, Androgens, Progesterone, Progestins

\(\uparrow\) GABA

Adiponectin, Leptin, etc
Glucose, Insulin, ghrelin

\(\downarrow\) GnRH drive

Appetite & energy balance

Kisspeptins
Aligned cognitions → ↓CRH / Cortisol → ↓GABA → Appetite & energy balance → ↑GnRH drive

↓CRH / Cortisol → Aligned cognitions

↓GABA → Androgens, Glucose, Insulin, ghrelin

↓GABA → Progesterone, Progestins

↓GABA → 5HT, E2

↓GABA → Kisspeptins

↓CRH / Cortisol → Energy balance

Energy balance → Adiponectin, Leptin, etc

Glucose, Insulin, ghrelin
Cognitions drive behaviors that then alter neuroendocrine secretory patterns
Psychometric inventories in EW vs FHA/SIA

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

Marcus MD et al. Fertil Steril 2001;76:310
Cognitive Behavior Therapy (CBT) for Functional Hypothalamic Amenorrhea (FHA) / Stress-Induced Anovulation (SIA)

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

16 sessions, 45 min each, over 20 weeks that 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 circulating cortisol in FHA/SIA

Michopoulos et al. Fertility & Sterility 2013
CBT reduced cortisol in the overnight sleep phase
Metabolic recovery / plasticity following CBT: ↑leptin and ↑TSH without weight gain
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
• Learning → behavioral / neuroendocrine / epigenetic plasticity
• May mitigate the impact of poor socioeconomic circumstances (social determinants of health)
• Has the potential to improve maternal and child health
• Has the potential to modify appetite and food preference
• May be initiated concomitantly with other interventions
Stress, Addiction, and Reproductive Function

- Stressors cluster and interact: multiple seemingly small stressors synergize and overwhelm coping mechanisms.
- Behaviors initiated in response to stressors (excessive exercise, rigid cognitions, stereotypy, undereating, emotional eating, substance use, etc.) may amplify neuroendocrine stress responses.
- Cognitive management of stress is designed to reduce maladaptive coping mechanisms and associated neuroendocrine alterations and replace with better coping skills and strategies.
- Chronic stress has profound acute and chronic health consequences for individuals and their offspring.
Embryo sex determines how the exposome alters the epigenome and signal transmission to future generations

Dunn GA, Morgan CP, Bale TL. Hormones and Behavior 2011; 59: 290 – 295
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**.
Maternal Diets Trigger Sex-Specific Divergent Trajectories of Gene Expression and Epigenetic Systems in Mouse Placenta

Displaying significant sexual dimorphism

Significantly dysregulated by maternal high fat diet (HFD)

Cortisol action is sex specific
Maternal stress differentially impacts male vs female fetuses

Using microarray analysis, 2000 more hormone responsive genes were detected in female than in male rats given a standard dose of a synthetic glucocorticoid

• 70 genes showed opposite changes in expression in males and females
• Inflammatory genes more suppressed in males
• Male rats had higher survival when given GC after exposure to infection

Duma et al. Sci Signal 3 ra74 2010
Cortisol blocks estradiol action

Over 10,000 genes were significantly regulated by dexamethasone (Dex) or estradiol (E2)

Most genes were regulated by both Dex and E2 (2527) vs Dex (187) and E2 (483)

Several hundred genes co-regulated by Dex and E2 were antagonistically regulated through the GC receptor (NR3C1) and ER-alpha (ESR1)

GC and ER-alpha receptors are required for transcriptional antagonism

Whirledge S et al. Biol Reprod 2013;89:66
Cortisol “hijacks” the cellular machinery required for full estrogen action and thereby acts as an “estrogen disruptor”

In addition to its effects, excess cortisol exposure from stress may act as an “estrogen antagonist”
Mechanisms by which “exposome” alters genome

- Variation in alleles (polymorphisms) resulting in modified mRNAs and proteins
- Variation in cis or trans regulatory (enhancer) DNA
  - (Science 2009; 326:1612)
- Alterations in promoter sequences
- Differential expression of co-activators and co-repressors modulate DNA transcription
- Altered imprinting
  - Methylation of DNA and histones
  - Acetylation of histones
- Micro RNA (miRNA) → altered gene transcription or translation
- Altered RNA trafficking / turnover → altered gene translation
- Transposons and endogenous retrovirus (ERVs)

Epigenetics of exposome

Differential DNA methylation and histone acetylation in twins across lifespan
Sex differences in reproductive health

- Stress causes infertility in women and men by inhibiting GnRH
- Stressors are sex specific
- The endocrine, molecular, and epigenetic “signature” of stressors is sex specific
- The neuroendocrine constellation that stressor elicit reflects the cluster of stressors
- The sex of the fetus and placenta modifies the impact of stressors during pregnancy
- Treatment of stress-related disorders requires sex- and gender-specific approaches
- The degree of plasticity is an open question
CONCLUSION
We have great opportunity to improve reproductive health by addressing the social determinants of mental health.

We can improve reproductive and thereby population health by:

- Understanding the link between stress, hormones, and adaptive versus maladaptive coping mechanisms
- Mitigating social determinants of poor parental health
- Translating knowledge about social determinants of health into therapeutic medical and social approaches
- Combining behavioral, pharmacological, and societal strategies to constrain stressors and their biological impact