Hot Issues in Women’s Health: Hormones, Menopause and Metabolism

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Learning Objectives

At the end of this session, the learner is expected to be able to:

- Recite the stages of the menopausal transition and relate these stages to specific hormone alterations.
- Predict the hormonal changes associated with changes in metabolism
- Understand how common menopausal symptoms influence metabolism apart from hormones
- Provide patients with evidence based guidelines to promote metabolic health in midlife

The Road to Menopause

![Diagram of the Road to Menopause]

- Pre-MT
  - Regular cycles
  - Median Age 47
- Early MT
  - Skipped cycles
  - Median Age 49
- Late MT
  - Prolonged amenorrhea
  - Median Age 49
Hormone Changes in the Pre- and Early Menopause Transition

- ‘Monotropic’ rise in FSH: first described in 1976 (Sherman)
- Erratic estradiol patterns (Santoro, 1996)
- Reduced progesterone production across the transition (Prior, Santoro, 2008)
- Shorter menstrual cycles (Klein, 2002)
- Less frequent ovulation

Transition Hormone Patterns

Breakdown of Usual Patterns

- Short cycles due to low inhibin and high FSH
- Follicle recruitment occurs in luteal phase
- New dominant follicles are ready to ovulate at menses
- Aberrant patterns appear to be associated with lower luteal P production
- Outcome=hormone roller coaster!
Individual Perimenopausal Woman

The Early Transition
- At least 1 menstrual period every 3 months
- Not an 'estrogen deficient' state
- Metabolic changes in the early MT likely due to:
  - Age related change in metabolism
  - Disruption of sleep

The Role of Sleep
- Experimental sleep restriction leads to:
  - Consumption of app 500 more calories/day
  - Gravitation to high salt/sugar/fat
- Physiologic sleep restriction may cause the same types of issues
- Midlife women susceptible to sleep apnea, snoring spouse, anxiety
- And hot flashes make all of that worse!

Spaeth, Am J Clin Nutr 2014; 100: 559
The Late Menopause Transition

- 60+ days of amenorrhea
- Estrogen deficiency predominates
  - Sleep gets even worse!
  - Hot flashes get worse—up to 85% of women affected
- SHBG and androgen metabolism shifts
- Changes in cardiometabolic markers become evident

Hot Flashes Across the Transition: SWAN

Adventitial Diameter in Relation to FSH/E2 in the MT
Changes in IMT and AD Across the MT

Testosterone, Estrogen and SHBG—It Gets Complicated

- Decreasing estrogen >> lower SHBG
- Increased Free Androgen Index
- More, not less bioavailable androgen
- Testosterone/estradiol molar ratio predicts incident metabolic syndrome (Torrens)
- FAI related to visceral fat (Janssen)
- Relationships persist after adjusting for HOMA and insulin resistance

Are Today's Women with PCOS Tomorrow’s Metabolic Train Wrecks?

- Women from SWAN who were hyperandrogenic and oligomenorrheic at baseline (Polotsky 2014 JCEM 99:2120):
  - 12 years follow up
  - Incident Metabolic Syndrome HR 1.4 [0.9-2.2] no higher than eumenorrheic normoandrogenic women
  - No increased risk in hyperandrogenic, eumenorrheic or normoandrogenic, oligomenorrheic women
Do Hormones Drive Metabolism or Vice Versa?

- SWAN cohort analyzed sequentially over 9 years and looked for lagged relationships between waist circumference and
  - FSH
  - Estradiol
  - Testosterone
  - SHBG

Wildman JCEM 2012; 97:E1695

Sequential Relationships Between Waist Circumference and FSH Using Standardized Estimates

Sequential Relationships Between Waist Circumference and Estradiol, Stratified by Menopausal Status Using Standardized Estimates
Sequential Relationships Between Waist Circumference and Testosterone Using Standardized Estimates

Sequential Relationships Between Waist Circumference and SHBG Using Standardized Estimates

Changes in Metabolism Associated with Menopause

- Decreased energy expenditure (mostly due to decreased physical activity)
- No change in insulin-stimulated glucose disposal
- Changes in BMR controversial
- Women aged 55-65 lose less weight (7kg) after bariatric surgery than women aged 20-45

The Role of Mood

- Adverse mood is a common menopausal symptom
- Risk for new onset major depression increases (16% prevalence)
- Anxiety follows a similar pattern

Depression and Anxiety

- Adverse mood most likely in the LATE transition
- Women with minimal pre-existing symptoms are most vulnerable (Soares, Drugs Aging 2013; 30:677)
- Experimental induction of perimenopause with VCD decreases P and DHT and produces anxiety symptoms in animal model (Reis, Psychoneuroendocrinology 2014: 49:130)

Adjusted OR for CES-D > 16 Across Visits 00-05 by Menopausal Status (p=.005)

Premenopause(reference group, 95% CI does not include 1 (Bromberger, J Affect Disord 2007)
Predicting First Major Depression Onset (n=42) Among 266 Women without Past MDD at Baseline

Mood and Metabolism
- Anhedonia, apathy >> decreased activity
- Disrupted sleep patterns
- Loss of diurnal cortisol rhythm
  - Increased visceral fat
  - Increased consumption of 'comfort foods'
- Emotional eating

What Can the Clinician Do?
- Treat key menopausal symptoms
  - Hot flashes
  - Poor sleep
- Detect and treat metabolic syndrome/weight management
  - Metformin
  - Lifestyle
- Detect and treat mood disorders
Exercise: An Essential Modifier

- Maintains weight
- Maintains endothelial function
- Improves insulin sensitivity
- Raises HDL

Mindfulness: An Essential Modifier

- May reduce BP
- Reduces stress
- Improves chronic pain
- Improves sleep (mindfulness CBT)


Hormones

- Reduce/eliminate hot flashes
- May improve sleep, vaginal symptoms, mood
- Reduces incident diabetes by 7% per year
Summary

- Midlife introduces a set of age and menopause related challenges that affect a woman's homeostasis.
- Sleep, mood, and physical activity may all be altered by the menopausal transition.
- Hormones may play a role in affecting metabolism directly but more likely indirectly.
- Clinicians can help their patients adapt.