Obesity and the Menopause

Vanessa M. Barnabei, MD, PhD
Professor and Chair
Department of Obstetrics and Gynecology
Educational Objectives

• Review normal menopausal transition
• Review health risks of obesity
• Learn variances of the menopausal transition in obese women
• Discuss variances of the risks and benefits of hormone therapy in obese women
• Learn approaches to symptom management in obese women

• Nothing to disclose
Obesity Epidemic

- Worldwide epidemic of obesity attributable to “passive overconsumption of energy”
- This is associated with:
  - Decreased education
  - Increased urbanization
  - Decreased energy expenditure
- Incidence of Type 2 DM has doubled in past 30 years
Obesity-Related Health Risks

- Obesity increases risk for:
  - Cardiovascular disease
  - Diabetes
  - Alzheimer’s dementia
  - Arthritis
  - Cancer
  - Depression
  - Sexual dysfunction
  - Urinary incontinence
  - Hysterectomy (uterine fibroids, abnormal bleeding and endometrial hyperplasia)
Obesity-related deaths continued to rise in 2015

According to the Los Angeles Times (4/4, Healy), “New statistics on death rates in the United States appear to confirm a grim prediction – that obesity is reversing decades of steady expansion in Americans’ life spans.” CDC data show that “in the first nine months of 2015, more Americans of all ages died of obesity-related diseases compared with the same period in 2014,” as “deaths from stroke ticked up 4%, chronic liver disease deaths jumped 3% and deaths attributed to heart disease and to diabetes rose by 1% each.” Meanwhile, deaths linked to “Alzheimer’s disease, which has been linked to midlife obesity, rose 19% over the year before.”
Obesity-Related Health Risks

- For CVD and death, impacts of obesity are greater in women than in men
- Metabolic syndrome (MBS) plays a large role in this
  - High central fat deposition
  - Insulin resistance
  - Dyslipidemia
  - Hypercoagulable and pro-inflammatory state
- 22% of all US women have MBS
- 40-50% of PMP women have MBS
Obesity and Cancer

- Obesity leads to an increased risk of:
  - Endometrial cancer
  - Breast cancer
  - Colon cancer
  - Thyroid cancer
  - Almost every other cancer you can think of
Obesity and Cancer

- Obesity causes a complex cascade of hyperinsulinemia and pro-tumorigenesis inflammation at the cellular and systemic levels.
- In breast tissue in the PMP woman, there is also an enhancement of aromatase activity and estrogen production that add to its vulnerability to cancer initiation and progression.
Obesity and Cancer

Overnutrition
Hyperinsulinemia
Hyperglycemia

Insulin/IGF-1 → PI3K → PIP3 → PDK1 → AKT → mTOR/Raptor → 4E-BP1 → eIF4E → VEGF, LDH, GLUT1 → Angiogenesis, Glycolysis

Leptin, STRAD/MO25 → LKB1 → AMPK1 → eNOS → NO → Angiogenesis

Cell cycle progression
Cell growth
Proliferation

Overnutrition
Hyperinsulinemia
Hyperglycemia

Glucose
Which of the following statements about perimenopausal vasomotor symptoms is not true?

A. 75% of women will experience vasomotor symptoms during the menopausal transition
B. Obese women are protected from vasomotor symptoms
C. Most women do not require medical management for vasomotor symptoms
D. Hot flashes are common in women who are still menstruating
Vasomotor Symptoms

- Vasomotor symptoms occur in about 75% of women
- Most women do not require medical treatment for vasomotor symptoms
- Vasomotor symptoms are common in women who are still menstruating
- Obese women are at greater risk of vasomotor symptoms than normal weight women
Estradiol in the Obese Woman

- Perimenopausal obese women may have lower serum estradiol than normal weight women.
- Postmenopausal obese women likely to have higher serum estradiol (and estrone) than normal weight women.
Perimenopausal Transition

- Obesity does not influence age at FMP (final menstrual period)
- At midlife (regardless of menopausal status), all women have increases in weight, adiposity and waist circumference
- After menopause, all women have increase in visceral fat deposition, which correlates with the rise in FSH, and leads to shift from gynecoid to android body type
How do we explain the discrepancy in CVD outcomes between observational and clinical trials of hormone therapy?

A. Clinical trials enrolled younger women
B. Different hormones were used in clinical trials
C. The timing of hormone therapy was different in clinical trials
Timing Hypothesis

- There is a “Critical Window” for benefit of HT
- Helps explain discrepancy between observational studies and RCTs
- Component 1: HT initiated early in menopausal transition will slow progression of early atherosclerosis
- Component 2: Beneficial effects of HT will be lost in later menopause when atherosclerosis is more advanced
Animal Studies

- Clarkson et al, working with cynomolgus monkeys, showed beneficial effect of estrogen on atherosclerosis progression
- Decrease in estrogen receptors (ER) in endothelium affected by atherosclerosis
- Estrogen may be anti-inflammatory with more ER and pro-inflammatory with fewer ER
- Pro-inflammatory effect leads to activation of MMPs (matrix metalloproteinases) and plaque disruption
Human Studies

- Hodis et al, NEJM 2016, ELITE Trial
- Assessed carotid-intima media thickness (CIMT), marker for atherosclerosis progression for oral E2 +/- vaginal P4 versus placebo x 5 years in early (< 6 years) and late (> 10 years) menopausal women
- Early menopausal estradiol users had significantly less progression of CIMT than non-users (0.0044 mm versus 0.0078 mm per year)
- Late menopausal estradiol users had similar progression of CIMT as non-users (0.0100 versus 0.0088 per year)
- CIMT is marker for CVD; actual events not reported
Pathogenesis of Coronary Artery Atherosclerosis of North American Human Females

Stage of Reproductive Life

Premenopause → Perimenopause → Postmenopause

15-25 yrs: ~5%  
25-35 yrs: ~15%  
35-45 yrs:  
45-55 yrs:  
55-65 yrs:  
> 65 yrs:  

Benefits of Endogenous E₂  
Primary Benefits of ERT/HRT  
Deleterious Effects of ERT/HRT  

MMP-9
What other factors may modify the risks and benefits of estrogen?

A. Route of administration
B. Metabolic syndrome
C. Concurrent Progestin use
D. Presence of vasomotor symptoms
Effect Modifiers

- **Progestogen**
  - WHI data suggest deleterious effect; other data conflicting; micronized P4 may be safer than synthetic progestogens

- **Metabolic Syndrome**
  - Wild et al, 2013; nested case-control study within WHI in women without prior CHD
  - CVD HR 2.26 for HT vs. placebo in women with MBS
  - CVD HR 0.97 for HT vs. placebo in women without MBS

- **Dose**
  - CHD benefit seen with even low doses
  - High doses may increase other risks
Obesity and Metabolic Dysfunction

**Lean with normal metabolic function**
- ↔ Inflammation
- ↔ Metabolic control
- ↔ Vascular function

**Obese with mild metabolic dysfunction**
- ↑ Inflammation
- ↓ Metabolic control
- ↔ Vascular function

**Obese with full metabolic dysfunction**
- ↑↑ Inflammation
- ↓↓ Metabolic control
- ↓ Vascular function

**Anti-inflammatory adipokines**
- Adiponectin
- SFRP5

**Pro-inflammatory adipokines**
- Leptin
- Resistin
- RBP4
- Lipocalin 2
- ANGPTL2
- CCL2
- TNF
- CXCL5
- IL-6
- NAMPT
- IL-18
Metabolic Syndrome

- Metabolic syndrome likely shifts atherosclerosis progression to younger age

- Obese PMP women with MBS have increased leptin and resistin and decreased adiponectin
Estrogen Effects on Glucose Homeostasis

• In normal weight women, estrogen improves insulin sensitivity and decreases abdominal fat deposition by about 7%
• Progestins blunt this affect, especially synthetic progestins
• Hormone therapy decreases incidence of new onset DM in PMP women
• Estrogen has other anti-diabetogenic effects
Which of the following is not a benefit of transdermal estrogen when compared to oral estrogen?

A. VTE risk
B. Symptom relief
C. Sexual function
D. Improved HDL cholesterol
Transdermal Better than Oral

- VTE risk
- Migraine headache
- Mammographic breast density
- Sexual function (libido)
- Growth hormone and IGF-1
- Triglyceride response
- Gallbladder disease
- Bile acid secretion and Biliary cholesterol saturation
Transdermal Estrogen

- Absorption of estrogen through the skin is very high
- Avoids first pass effect
  - No change in SHBG or other binding globulins
  - No change in E2:E1 ratio
- Allows for more convenient dose titration and weaning
Route of Administration

• Oral estrogen leads to increased fat mass, decreased IGF-1, increased GH and decreased lean body mass (all bad!)
• Transdermal estrogen causes no change in body mass or leptin and increases adiponectin (all good!)
## Route of Administration Matters

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Hormone Therapy in the Obese Woman

- Assess for risk factors of cardiovascular disease, even in perimenopausal women
- CVD may be present at younger ages in obese women, so counsel accordingly
- In young women without MBS, benefits of HT in very symptomatic women may outweigh risks for short term therapy
- Use transdermal estrogen to minimize risks to CV system (regardless of weight)
HT Alternatives

- SSRI/SSNI: many studies support benefit, off-label
- Low-dose mesylate salt of paroxetine 7.5 mg (+FDA)
- Gabapentin and Pregabalin, off-label
- SERMS “estrogen agonist/antagonist with tissue selective effects”:
  - Ospemifene: approved for VVA, may make VMS worse; probable breast/endometrial safety
  - CEE+bazedoxifene, may relieve need for progestogen but still has risks of oral estrogen
  - Tibolone: endorsed by Spanish Menopause Society for VVA and VMS
- Dosing of these medications same in obese and normal weight women
Obesity and Health

- World-wide epidemic of obesity shows no signs of abating
- Health effects of obesity may last for generations due to epigenetic changes
- Obesity is shifting onset of postmenopausal diseases into the later reproductive years
- Health care providers should not “normalize” obesity and its effects but encourage patients to address it and help them find a path towards better health