Obesity and Reproduction

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Learning Objectives

At the end of this lecture the listener is expected to be able to:

• Enumerate the multiple adverse reproductive outcomes attributed to female obesity

• Develop a strategy that will help obese patients modify behaviors to optimize fertility outcomes
Disclosures

• Investigator initiated grant support: Bayer
• Stock option: Menogenix
I. Obesity is linked to adverse reproductive outcomes and a relatively hypogonadotropin hypogonadal (HH) phenotype in women.
Prevalence of Obesity 1999 (BMI > 30)
Prevalence of Obesity 2008 (BMI > 30)
Reproductive Phenotype of Obesity

• Rarely examined until recently:
  – Longer cycles, lower P4 production, luteal phase defect phenotype (Sherman, JCEM 1974; 39:145)
  – Grenman (JCEM 1986; 63:1257): longer cycles, low P4, improvement with weight loss
  – Longer time to pregnancy
  – More pregnancy complications
  – Small sample sizes, descriptive studies
Adolescent obesity & lifetime fertility – SWAN

<table>
<thead>
<tr>
<th>HSBMI, kg/m²</th>
<th>Nulliparity</th>
<th>Nulligravidity</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;18.5</td>
<td>1</td>
<td>1</td>
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<tr>
<td>18.5-24.9</td>
<td>1.4 (1.0-1.9)</td>
<td>1.3 (0.9-1.9)</td>
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<tr>
<td>25.0-29.9</td>
<td>1.7 (1.0-2.8)</td>
<td>2.0 (1.1-3.6)</td>
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<tr>
<td>≥30</td>
<td>4.0 (2.1-7.7)</td>
<td>5.1 (2.5-10.5)</td>
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Add Danish Slide of BMI vs Fertility
Verifying the Phenotype

• SWAN the Study of Women’s Health Across the Nation
• Daily Hormone Study: 979 premenopausal women who collected one menstrual cycle of daily, first morning voided urine
• Data assayed for LH, FSH E1c and Pdg
• 768 had ovulatory cycles
• Cycles examined by BMI category
Increasing BMI is Associated with Lower Reproductive Hormones

Santoro N, JCEM 2004; 89:2622
Obesity is Associated with Relative Hypogonadotropin Hypogonadism

• Reduced LH pulse amplitude
• Reduced LH response to GnRH
• Lower levels of FSH, E2, P during ovulatory menstrual cycles
• Longer menstrual cycles by about 5 days on average than normal weight women
• Increased time to pregnancy, pregnancy loss, and adverse perinatal outcomes
Why Is This Worth Studying?

• Obesity is difficult to treat, and it’s not even clear that weight loss is beneficial for reproduction in obese women
• Maternal obesity gets transmitted to offspring
• Identifying the factors responsible for reproductive dysfunction may also provide a metabolic course correction and avoid some of obesity’s downstream consequences in pregnancy
Obesity is Transmitted Transgenerationally

• Obese mothers are TWICE as likely to have children diagnosed with obesity by age 2
  (Whitaker RC, Pediatrics 2004; 14:29)

• Fetal programming known to occur in utero

• Does the preconceptual reproductive endocrine milieu of obesity hasten/promote adverse fetal metabolic programming?
Why Are Menstrual Cycles Abnormal in Obesity and Does Weight Change Help?

• Funded R21 to investigate LH pulsatility in obesity, before and after weight loss surgery

• 23 women studied preoperatively; 6 postoperatively
  – 12 hour frequent blood sampling study to assess LH pulsatility
  – One pre op and one post-op cycle of first morning voided urine
  – Normal weight controls (historic)
Obese Women Have Decreased LH Pulse Amplitude

Representative LH Pattern in Normal versus Obese Woman

Jain A, JCEM 2007; 92:2468
Surgically Induced Weight Loss Normalizes Obese Pattern of LH Secretion

LH Patterns Pre- and Post-Op

Sample (0-720 min)
Surgical Weight Loss Improves the Reproductive Hormone Profile

Additional Deficits in the HPO Axis

• Circulating adipocytokines, inflammatory factors and free fatty acids (FFAs) have all been implicated in causing dysfunction at the level of the corpus luteum and follicle.
• The inflammatory burden may be the most fruitful area to attack to improve the reproductive outcomes in obese women.
Evidence for ‘Lipotoxicity’

- Obese vs OW and MOD women: more FF Ca++, more ER stress marker expression (ATF4)

(Wu, Endo 151: 5438, 2010)
FF Triglycerides, Androgen Index, and CRP in Women With Varying BMI (N=97)

FF Insulin, Glucose, and Lactate in Women With Varying BMI (N=97)

A

B

C

D


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Basic Evaluation

• Calculate BMI: http://www.nhlbisupport.com/bmi/

• Estimate adult weight gain (What did you weigh when you were 18?)

• Metabolic assessment:
  – Waist circumference
  – BP
  – Fasting lipid panel, glucose or HgbA1c
  – Thyroid screen (TSH) as appropriate
  – Consider LFTs: NAFLD
Risk Modifiers

- Fitness: attenuates mortality curves at all BMIs
- Fatness and distribution: Body fat content may be more important than BMI; ‘metastatic fat’
- Adult weight gain: strong predictor of morbidity and mortality
- Presence or absence of BMI-related comorbidity
- Are there metabolically healthy obese women who require less intensive intervention?
The Metabolic Syndrome

AHA Definition: at least 3 of the following:

– Waist >35” or 31.5” for Asian women
– TGs > 150 mg/dl
– HDL < 50 mg/dl
– BP > 130/85 or on medication
– Fasting glucose > 100 mg/dl
Appetite Regulation

• No evolutionary advantage to satiety in a world where food is scarce
• Human appetite expands to accommodate available food sources
• Economic incentives to sell more food
• For every satiety peptide (leptin) there are 10 orexigenic peptides!
• Appetite regulation through SSRI/SNRI agents largely banned in US by FDA
Sleep, Weight, Metabolism and Menopause

• A mysterious relationship
• RMR decreases by 25% over a woman’s 5th decade of life
• Functional limitations are present in almost 30% of women by age 45!
• The menopause transition is associated with worse sleep
• Poor sleep is associated with poor food choices, weight gain and daytime fatigue
Sleep Disorders in Women

- No one admits to snoring
- Assess for RLS and sleep apnea
- Assess for daytime sleepiness
- Assess for depression
- Short term, new generation sleep aids have low addiction potential
Weight Loss Trials in Obese Women

• No one diet plan is superior

• Exercise is critical for maintenance
  – Up to an hour per day for obese-reduced women

• Consider supplementation with medication
  – Orlistat: extra weight loss of 8-12lbs
In the Highly Motivated...

• Small, multiple lifestyle changes
  – Assess readiness for change
    • Pre-contemplation > Contemplation > Preparation > Action > Maintenance
  – Emphasize fitness: it is easier to achieve for many
  – Caloric restriction—eliminate macronutrients or total calories

• Frequent follow up
• Consider patient contract
When to Consider Surgery

- BMI > 35 kg/m²
- BMI > 30 kg/m² but < 35 kg/m² with co-existing morbidity:
  - T2DM
  - Hypertension
  - NAFLD
- Patients undergoing surgical weight loss are advised to wait at least 1 year before trying to conceive
Summary

- The obesity epidemic is leveling off but remains a major burden to the health of American women.
- Women are especially vulnerable when they are trying to conceive.
- Physicians and health care providers underestimate their influence in helping patients undergo behavioral changes necessary for weight management.