Obesity and Infertility

Nanette Santoro, MD
Professor and E Stewart Taylor Chair
Department of Ob/Gyn
University of Colorado at Denver

Background

- Obesity associated with reduced LH/FSH and lower E/P (women) and T (men) in a dose dependent fashion
- Reduced monthly fecundability, increased pregnancy wastage, and reduced response to ART procedures and stimulation in women
- Mechanisms not known but central hypothalamic drive one suspected locus of failure

Prevalence of Obesity 1999 (BMI>30)
Prevalence of Obesity 2008 (BMI>30)

Probability of Conception With Increasing BMI (adjusted for age, smoking, race, education, occupation and study centre)


SWAN
- Community based cohort study of 3302 women aged 42-54 at baseline
- Annual measurements of blood, physical measures and surveys
- Now in its 11th year of follow up
Lifetime Nulliparity is Increased in Obese Women

- SWAN baseline cohort:
  - What was your high school weight?
  - Correlated with fertility outcomes

Adolescent obesity & lifetime fertility

- SWAN

<table>
<thead>
<tr>
<th>HSBBMI, kg/m²</th>
<th>Nulliparity</th>
<th>Nulligravidity</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;18.5</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>18.5-24.9</td>
<td>1.4 (1.0-1.9)</td>
<td>1.3 (0.9-1.9)</td>
</tr>
<tr>
<td>25.0-29.9</td>
<td>1.7 (1.0-2.8)</td>
<td>2.0 (1.1-3.6)</td>
</tr>
<tr>
<td>≥30</td>
<td>4.0 (2.1-7.7)</td>
<td>5.1 (2.5-10.5)</td>
</tr>
</tbody>
</table>

SWAN: the Daily Hormone Study

- 848 women in daily hormone substudy completed a cycle of daily urinary hormone sampling
  - Collections were from menses to menses
  - LH, FSH, estrone conjugates and pregnanediol glucuronide measured
Whole cycle hormones of ovulatory women in the SWAN Baseline daily hormone study by BMI (n=632)

<table>
<thead>
<tr>
<th>Hormone (per mgCr)</th>
<th>&lt;25 kg/m²</th>
<th>&gt;25 kg/m²</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LH (mIU)</td>
<td>79</td>
<td>50.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FSH (mIU)</td>
<td>467.8</td>
<td>385.8</td>
<td>&lt;0.003</td>
</tr>
<tr>
<td>E1c (ng)</td>
<td>1369.6</td>
<td>1171.6</td>
<td>=0.006</td>
</tr>
<tr>
<td>Pdg (ug)</td>
<td>60.8</td>
<td>42.0</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Daily levels of urinary hormones in women with BMIs <25 kg/m², 25-29.9 kg/m², and >=30 kg/m²

Serum FSH, Estradiol and DHEAS very inversely with BMI in SWAN (Randolph, JCEM 2003; 88:1516)
Androgens vary positively with BMI in SWAN (Santoro, JCEM 2005; 90:4836)

...SO WHY DON’T THEY GET PCOS?
Potential Sources of T in Obese Women

- Adipose tissue: 17 beta HSD increased in adipose tissue (Quinkler)
- Ovary: would secrete more T in the presence of less LH
- Adrenal gland
- Reduced T clearance

Type 5 17BHSD mRNA is Greater in SC vs Omental Fat

Hypothesis

- Increased T has a dichotomous effect on the HPO axis in women
  - If PCOS-prone: increased HP sensitivity, increased LH
  - If not PCOS-prone: provides negative feedback signal to HP axis

- IHH men given testosterone and ‘GnRH-clamped’
- Reduced pituitary response to GnRH after T
- Response largely (but not completely) eliminated with aromatase inhibition
- Does CNS aromatase influence T sensitivity?

Evidence for Decreased Central Neural GnRH Drive with Obesity

- Women:
  - Lower LH/FSH in women with PCOS as obesity increases
  - Higher T, lower E2 and SHBG regardless of PCO/non-PCO status
- Men:
  - Lower LH/FSH with increasing BMI
  - Lower T, higher E2, higher SHBG

What is the Pattern of Daily Hormones and Pulsatile LH Secretion in ‘Simple’ Obesity?

- Planned study of daily urinary hormones and LH pulsatility (subsample) in women before and after bariatric surgery
- Assumptions: at least partial reversal of obesity-induced reproductive changes would be observed after weight stabilization and 25% weight loss
Representative LH Pattern in Normal Weight vs Obese Woman

Jain A, JCEM 2007; 92:2468

Daily Hormones Pre- and Post-Bariatric Surgery
- Women start out very large (BMI>35)
- All lost at least 25% of starting body weight
- Mean time to follow up app. 6 months
- Difficulties:
  - They often don’t achieve a near normal body size after surgery
  - Follow up and follow through cause lots of attrition
  - Very large size of women at outset causes concern about ‘representativeness’ of model
Table 2a. Cycle Parameters Pre- and Post-Op

<table>
<thead>
<tr>
<th></th>
<th>Controls (n=14)</th>
<th>High BMI Pre-Op (n=22)</th>
<th>High BMI Post-Op (n=6)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cycle length (d)</td>
<td>27.6 ± 3.4</td>
<td>29.5 ± 6.0</td>
<td>27.2 ± 2.8</td>
<td>0.2</td>
</tr>
<tr>
<td>Peak LH (mIU/mgCr)</td>
<td>40.8 ± 29.4</td>
<td>27.6 ± 12.4</td>
<td>43.7 ± 10.6</td>
<td>0.007*</td>
</tr>
<tr>
<td>LH (mIU/mgCr)</td>
<td>166.0 ± 54.0</td>
<td>166.5 ± 24.2</td>
<td>292.1 ± 73.6</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>FSH (mIU/mgCr)</td>
<td>141.3 ± 63.1</td>
<td>149.4 ± 33.5</td>
<td>178.4 ± 89.3</td>
<td>0.12</td>
</tr>
<tr>
<td>1st 7 days LH (mIU/mgCr)</td>
<td>26.4 ± 23.6</td>
<td>22.0 ± 23.0</td>
<td>38.2 ± 16.7</td>
<td>0.17</td>
</tr>
<tr>
<td>1st 7 days FSH (mIU/mgCr)</td>
<td>44.5 ± 16.8</td>
<td>47.4 ± 19.7</td>
<td>42.0 ± 17.4</td>
<td>0.55</td>
</tr>
</tbody>
</table>

Extreme Obesity
- Women with BMI > 35 kg/m²
- Diet and exercise unlikely to work
- Ask about prior attempts
- Screen for eating disorder
- Correct endocrinopathies
- Screen for diabetes
- Consider surgical therapy
Bariatric Surgery

- Gastric reduction (lap banding, stapling): achieves initial weight loss, decreases intake and increases satiety
- Malabsorptive procedure (Roux en Y): maintains long term weight loss by decreasing absorption

It Works

- Bariatric surgery: the most effective treatment for morbid obesity
  - 1998 = 13,386 weight loss surgeries
  - 2006 > 200,000
- CMMS: Primary treatment for T2DM when BMI>35
- Types of Operations:
  - Roux en Y Gastric Bypass - most common in US
  - Laparoscopic Adjustable Gastric Band
  - Biliopancreatic Diversion

Gastric Banding

- Laparoscopic Gastric Band: purely restrictive
- Complications: less frequent than with Gastric Bypass; mortality 0.002%.
  - band slippage
  - reservoir deflation/leak
  - failure to lose weight
  - persistent vomiting
  - acid reflux.

Most Common Procedures: Roux-en-Y

Gastric Bypass (Mason)
- Staple line across the top of the stomach modified into Roux-en-Y procedure.


Warning: These Procedures Are Drastic
- Gastric reduction: stomach volume = 50 ml or < 2 oz! Normal adult stomach holds app. 1 quart or 32 ounces!
- Roux Limb: typically 75-150 cm. The longer the limb malabsorption.
- Typically results in long-term weight loss of at least 50% of excess body weight.
- Bypass gastric banding in US

Complications: 5-10% (Mortality <1%)

<table>
<thead>
<tr>
<th>Early Complications</th>
<th>Late Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leaks</td>
<td>Stomal Stenosis</td>
</tr>
<tr>
<td>Deep vein thrombosis/embolism</td>
<td>Anemia</td>
</tr>
<tr>
<td>Roux-en-Y obstruction</td>
<td>Vit B12 deficiency</td>
</tr>
<tr>
<td>Atelectasis (Lung collapse)</td>
<td>Ca++ deficiency/osteoporosis</td>
</tr>
<tr>
<td>Wound infection</td>
<td></td>
</tr>
</tbody>
</table>
Biliopancreatic Diversion (BPD)

- Typically for people with BMIs ≥ 50.
- Two components:
  - Reduce stomach size (immediate weight loss)
  - Long limb Roux-en-Y anastomosis
  - The shortened active short intestine (20") > malabsorption>>>>sustained weight loss as stomach capacity increases.

BPD: Complications

- Disadvantages: loose, foul smelling stools, stomal ulcers, and gas.
- Complications: protein malnutrition (12%), anemia (35%) and bone demineralization (25-50%).
- Calcium and vitamins, particularly Vitamin D supplements required lifelong.
- Associated with more pregnancy related complications

Post-Op Considerations

- Weight loss of 25-50% initial body size expected
- Rapid weight loss within first 6-12 months
- Currently unclear when to time pregnancy after weight loss surgery
  - Suggest 12-24 months
  - Need time to assess for surgery complications
Summary

- Obesity is associated with a unique reproductive phenotype of relative hypogonadotropic hypogonadism
- Decreased amplitude but not frequency of pulsatile LH secretion is seen
- Decreased fecundability, increased pregnancy wastage and peripartum complications are all increased with increasing BMI

Summary

- For lesser degrees of obesity and people who have not previously tried to lose weight, lifestyle management is the first line treatment
- For more extreme obesity, especially when comorbidities exist, surgical methods are more appropriate

Acknowledgements

Santoro Lab
- Akas Jain, MD
- Alex Polotsky, MD, MSc
- Dana Rochester, MD
- Barbara Isaac, RN
- Goli Adel, BS
- Gohar Zeitlian, MD
- Cheryl Hickmon, BS

Collaborators
- Maureen Charron, PhD
- KMJ Menon, PhD
- Susan Appt, DVM, PhD
- Satu Kuokkanen, MD, PhD
- Sara Berga, MD
- Tammy Loucks, MS