INFERTILITY IN THE U.S.

- 10–15% of couples face infertility
- One of the most common health concerns among young adults
- On average, couples have 25%–30% chance of conceiving each cycle if the woman is in her 20s–30s
- Other factors include oviduct blockage or ovulation issues for the woman or environmental exposures (smoking)
- Approximately 1/3 of infertility is related to male-related factors

Background on Infertility from the American Society of Reproductive Medicine

(Women)
WEIGHT AND FERTILITY

- Underweight and reduced fertility (Frisch, 1987)
- Distance runners and ballet dancers and menstrual irregularities
- Primary or secondary amenorrhea
- Longer inter-pregnancy intervals
- Earlier menopause

- For a reference, percent body fat estimated for:
  - Menarche ~17% fat/body weight
  - Maintenance of reproductive ability ~22% fat/body weight
- Compare to recent NHANES 1999–2004 percent body fat estimates (Li, 2009)

Background on Women

NHANES %BODY FAT (1999-2004)

<table>
<thead>
<tr>
<th>Total</th>
<th>Mean</th>
<th>SE</th>
<th>25th</th>
<th>50th</th>
<th>75th</th>
<th>&gt;75</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18-24</td>
<td>20.5</td>
<td>0.3</td>
<td>19.1</td>
<td>21.4</td>
<td>22.8</td>
<td>24.3</td>
</tr>
<tr>
<td>25-29</td>
<td>21.7</td>
<td>0.3</td>
<td>20.8</td>
<td>22.3</td>
<td>23.9</td>
<td>25.3</td>
</tr>
<tr>
<td>30-34</td>
<td>22.9</td>
<td>0.3</td>
<td>22.0</td>
<td>23.5</td>
<td>25.0</td>
<td>26.0</td>
</tr>
<tr>
<td>35-39</td>
<td>24.4</td>
<td>0.3</td>
<td>23.3</td>
<td>24.8</td>
<td>26.2</td>
<td>27.2</td>
</tr>
<tr>
<td>40-49</td>
<td>26.3</td>
<td>0.3</td>
<td>25.2</td>
<td>26.8</td>
<td>28.6</td>
<td>29.8</td>
</tr>
<tr>
<td>&gt;50</td>
<td>28.0</td>
<td>0.3</td>
<td>26.9</td>
<td>28.5</td>
<td>30.2</td>
<td>31.4</td>
</tr>
</tbody>
</table>

NHANES %BODY FAT (1999-2004)
TERMINOLOGY

- **Infertility**
  - Inability to bear a live born infant

- **Subfertility or reduced fertility**
  - Evidence of the ability to bear a live born infant, though delayed in conception

- **Fecundity**
  - Ability to conceive a child

- **Fecundability**
  - Probability of conceiving a child during one ovulatory cycle given sexual intercourse and discontinuation of contraceptives

EXCESS WEIGHT AND REPRODUCTION

- Obesity associated with impaired fertility in women
- Reduced fecundity, even among women with regular menses (Gesink, 2007);
  - Adj OR = 0.92 and 0.82, overweight and obese, respectively
- Pre-pregnancy obesity and stillbirth (Chu, 2007);
  - OR = 1.47 and 2.07, overweight and obese, respectively
- Interpregnancy weight gain associated and stillbirth (Whiteman, 2011);
  - Increased risks of cesarean delivery, assisted delivery, structural malformations such as nervous system, craniofacial, and cardiac (Balaha, 2012)

WEIGHT LOSS AND REPRODUCTION

- Weight loss among women with subfertility associated with polycystic ovarian syndrome shows resumption of ovulation (Kuchenbecker, 2011)
- Resumption of ovulation with consistent loss of intra-abdominal fat
- After bariatric surgery, rates of maternal complications and neonatal outcomes were significantly reduced (Maggard, 2008);
  - GDM, pre-eclampsia, macrosomia
- Currently, no trials or strong observational evidence of good fecundability after bariatric surgery

EXCESS WEIGHT AND REPRODUCTION

- Couples have higher risk of subfertility if both were obese (Ramlau-Hansen, 2007);
  - Adj. OR = 1.78 of subfertility if woman was obese and 1.49 if man obese regardless of the other, however, when both were obese 2.74 compared to women both were normal weight.

### Table 5: Odds ratios (OR) for subfertility before pregnancy of > 12 months according to categories of men's and women's BMI

<table>
<thead>
<tr>
<th>Weight</th>
<th>Men's BMI (kg/m²)</th>
<th>Women's BMI (kg/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;18.5</td>
<td>1.00 (Ref)</td>
<td>1.00 (Ref)</td>
</tr>
<tr>
<td>18.5-24.9</td>
<td>1.00 (Ref)</td>
<td>1.00 (Ref)</td>
</tr>
<tr>
<td>25.0-29.9</td>
<td>1.00 (Ref)</td>
<td>1.00 (Ref)</td>
</tr>
<tr>
<td>30.0-34.9</td>
<td>1.00 (Ref)</td>
<td>1.00 (Ref)</td>
</tr>
<tr>
<td>≥35.0</td>
<td>1.00 (Ref)</td>
<td>1.00 (Ref)</td>
</tr>
</tbody>
</table>

Table 5: Odds ratios (OR) for subfertility before pregnancy of > 12 months according to categories of men's and women's BMI

Background on Women and Men
MEN
WEIGHT AND FERTILITY

MOBA STUDY OF FERTILITY

- Cohort study of pregnant women
  - Women throughout Norway
  - Retrospectively collected time to pregnancy
  - Asked women to report her male partner's height and weight, and BMI was calculated

- Determined whether men's BMI was associated with increased time to pregnancy, after accounting for:
  - Women's BMI, age (men and women), smoking (men and women), and frequency of sex
  - 23,986 couples included in the analysis

POTENTIAL MECHANISMS

- Obesity has been associated with:
  - Reduced sexual desire (Hammoud, 2009);
  - Erectile dysfunction (Hammoud, 2009);
  - Reduced number of children (Pauli, 2008)

- These factors may all be related to depressed androgen production in obese men

  - Adipose tissue may increase estrogen levels by conversion of androgens

EXCESS WEIGHT AND REPRODUCTION

- Reduced fertility associated with increases in men's BMI in a large sample of couples (Nguyen, 2007)
MEN’S BMI AND SEMEN QUALITY

• Young men’s BMI associated with poorer semen parameters among military recruits (Jensen, 2004);
  • Both high and low BMI adversely associated with semen quality (u-shaped curve);
  • Concentration and total sperm were reduced by 21.6% and 23.9%, respectively, among men with BMI > 25;
  • Total testosterone, SHBG, inhibin B inversely associated with BMI;
  • Estradiol and FAI increased with increasing BMI

Basic studies

CONCLUSIONS

• Body of literature supports that excess weight in men, similar to that found in women, reduces fertility potentially through:
  • Increased estrogenization (alteration in reproductive hormones) that reduces semen and sperm production;
  • Poor gamete quality (poor sperm morphology, motility);
  • Increased body temperature (?);
  • Storage of toxins in adipose (?);
  • Deficiencies in micronutrients associated with normal sperm production (?)

Basic studies

GAP IN KNOWLEDGE

• Body of literature does not answer whether weight loss in men confers benefit to improving fertility
  • There is some evidence that weight loss may improve:
    • Circulating testosterone level
    • Improve sexual functioning
  • However, it is unclear whether the semen parameters benefit after weight loss
    • Some evidence indicates a reduction in semen characteristics (Sermonda, 2012; Lazaros, 2012)

Basic studies

BARIATRIC SURGERY & HORMONES

• Bariatric surgery can improve reproductive hormones within 6 months (Facchiano, 2012)
  • Age is an important confounder; those <35 y were saw significant improvement, and age was the lone predictor of post-surgery total testosterone

Basic studies

• Bariatric surgery improved reproductive hormones and sexual functioning up to 20 months surgery (Reis, 2012)
  • 10 morbidly obese men randomized into a trial control had no intervention;
    • Run-in behavioral weight loss intervention for 4 months; no change in reproductive hormones at that point;
  • No significant changes in semen parameters

Basic studies
**BARIATRIC SURGERY & SEMEN**

- Unclear whether weight loss after bariatric surgery was associated with poorer semen quality
  - Two studies found an association with poor semen quality (Lazaros, 2012; Sermondade, 2012)
  - Two studies found no sustained reduction in semen quality with time after surgery (Reis, 2010; Legro, 2014)
- Bariatric surgery presents different weight loss outcomes than lifestyle intervention
  - Greater weight loss
  - Shorter time
  - Restricted diets

**OBSERVATIONAL COHORT**

**WEIGHT LOSS AND MEN’S FERTILITY**

**OBSERVATIONAL COHORT OF MEN AND WEIGHT LOSS**

- Observational cohort in Denmark of n=43 men with BMI > 33 (Hakonsen, 2011)
  - Men aged 20 - 59 y enrolled in a behavioral weight loss program lasting 14 weeks
  - Non-randomized
  - Not a part of the research study, with no control group
  - Mean % weight loss = 15%
- Weight loss associated with increases in:
  - Total sperm count, semen volume
  - Testosterone and SHBG
  - Those with the most weight loss saw significant increases in count and morphology

**BEHAVIORAL INTERVENTION TRIAL**

**WEIGHT LOSS AND MEN’S FERTILITY**

**SIGNIFICANCE OF WEIGHT LOSS**

- Identification of a modifiable behavioral change that may improve reproductive hormones may enhance:
  - Men’s and couple’s fertility
  - Reproductive hormones and semen characteristics
  - Identify a responsive biomarker to motivate weight loss
- Thus providing biological mechanism data on what factors of weight loss may influence reproductive hormones and sperm production

**OBESITY PREVENTION CENTER PILOT**

**Adiposity and Infertility Study (ADONIS)**

- Pilot study of a clinical trial among obese men to determine:
  - Does behavioral lifestyle weight loss intervention among young, obese men improve reproductive parameters
  - Reproductive hormones
  - Semen characteristics
ADONIS STUDY

<table>
<thead>
<tr>
<th>Personnel</th>
<th>Role</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jennifer Unde</td>
<td>Intervention</td>
</tr>
<tr>
<td>Christopher DeJonge</td>
<td>Biological specimens, clinic liaison</td>
</tr>
<tr>
<td>J. Bruce Redmon</td>
<td>Interpretation</td>
</tr>
<tr>
<td>Cynthia Bjerk</td>
<td>Nutrition intervention</td>
</tr>
<tr>
<td>Rachael Turner</td>
<td>Study coordinator</td>
</tr>
<tr>
<td>Michael Finke</td>
<td>Research Assistant</td>
</tr>
<tr>
<td>Koryn Ha</td>
<td>Research Assistant</td>
</tr>
</tbody>
</table>

ADONIS PILOT

- Obese men (BMI >30) were enrolled
- Men with known diabetes were excluded
- Randomized into intervention or control;
  - Intervention: 1-to-1 counseling, 1x per week for 6 months, then 1x every other week;
  - Control: No intervention
- Intervention group members worked with Cindy to set goals on dietary intake and physical activity;
  - Weighed-in each week on a standard scale

ADONIS DATA COLLECTED

- All participants provided the following at baseline, 6 months, and 12 months:
  - Epidemiology Clinic Research Center
    - Survey data on basic demographic and behavioral variables;
    - Survey data on sexual functioning (International Index of Erectile Function, IIEF-5);
    - Anthropometric measurements;
      - Height, weight, abdominal circumference, hip circumference;
      - TANITA measurements (i.e. % body fat)

ADONIS BIOLOGICAL SPECIMENS

- Fairview Riverside Reproductive Medicine Center
- Semen sample;
  - Blood sample (6 mls, 1 tube) for reproductive hormones:
    - estradiol, testosterone, SHBG, and FAI

SEMEN ANALYSIS

- Men abstain from ejaculation for at least 48 hours;
- The following are the specific assessments in the semen analysis:
  - Semen: liquefied, viscous, agglutination, pH, volume
  - Sperm:
    - count (concentration, total number);
    - motility (progressive/non-, immotile, total progressive);
    - morphology (vitality, morphology, mUnd cell, immature, cell fragments, normal/abnormal, head defect, tail defect)
    - Seminal reactive oxygen species (ROS)

RECRUITMENT

- Men were actively recruited from:
  - University and Fairview community;
  - Local community (newspaper ads);
  - Local male-dominated fields (flyers to firehouses and police stations);
  - Social media
- Aimed to have 20 men in each arm
  - Final count was 27 men in total
  - 14 intervention and 13 control men
  - 19 men completed the 6 month visit
  - 9 men completed the 12 month visit
ADONIS FEASIBILITY FINDINGS

• Requirement to provide semen sample did not deter many potential participants;
  • Only 1 inquiring male refused due to semen sample request;
  • No male refused to provide a semen sample after enrollment;
  • Largest deterrent was commitment to nutrition visits

• Collaboration with the RMC worked
  • But expensive!

ADONIS FEASIBILITY FINDINGS

• Recruitment was difficult
  • Potentially due to pilot nature;
  • Building relationships with the community could help;

• A need to better communicate the benefits of the ‘intensive’ behavioral weight loss meeting schedule

• Should recruitment be an issue improved methods for higher retention is warranted

ADONIS RESEARCH FINDINGS

Median weight loss was 2.2 kg for controls and 10.7 kg in the intervention (p = 0.004).

Median change in testosterone in the intervention group:
  • r = 0.68, p = 0.09

Median change in SHBG in the intervention group:
  • r = 0.94, p = 0.001

Median change in FAI consistent with previous knowledge but not significant in the intervention group:
  • r = -0.38, p = 0.41

No difference in estradiol in either group

ADONIS RESEARCH FINDINGS

• Behavioral weight loss may improve reproductive hormones at 6 months:
  • Median change in testosterone in the intervention group
  • r = 0.68
  • Median change in SHBG in the intervention group
  • r = 0.94
  • Median change in FAI consistent with previous knowledge but not significant
  • r = -0.38

No difference in estradiol in either group

ADONIS LIMITATIONS

• Small size;
  • Particularly after attrition;
  • High variability of semen analyses;

• Convenient sample;
  • Therefore recruitment rates cannot be determined;
  • Anecdotally, frequency of intervention was a barrier

• Homogeneity of participants;
  • Unable to determine differences by race, for example
ADONIS CONCLUSION

- Successful framework to provide lifestyle behavioral intervention in one location (ECRC) and biomedical evaluation in another (Fairview Riverside);
- Young men would provide semen samples;
- Strong evidence that lifestyle behavioral weight loss is achievable in this sample of young, obese men;
- Weight loss was associated with improved hormone parameters;
- Recruitment was difficult;
- Attrition was high

Pilot study

OTHER FACTORS OF SPERM QUALITY

- Growing body of evidence indicating specific micronutrients, also associated with excess weight and weight loss, are associated increased or poor sperm quality
  - Antioxidants;
  - Fats

MICRONUTRIENTS

- Growing body of evidence indicating specific micronutrients, also associated with excess weight and weight loss, are associated increased or poor sperm quality
  - Antioxidants;
  - Fats

SPERMATOGENESIS

ANTIOXIDANTS AND OBESITY

- Absorbed levels of vitamins (serum levels) reduced after weight loss surgery, despite vitamin-mineral supplementation (Donadelli, 2012)

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Absorbed values</th>
<th>Total</th>
<th>3 mo.</th>
<th>6 mo.</th>
<th>12 mo.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin (mg/dL)</td>
<td>&lt;1.00</td>
<td>84.8</td>
<td>84.8</td>
<td>84.8</td>
<td>84.8</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>&gt;200</td>
<td>37.9</td>
<td>37.9</td>
<td>37.9</td>
<td>37.9</td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>&gt;20</td>
<td>62.1</td>
<td>62.1</td>
<td>62.1</td>
<td>62.1</td>
</tr>
<tr>
<td>Transferrin (mg/dL)</td>
<td>&gt;150</td>
<td>350</td>
<td>350</td>
<td>350</td>
<td>350</td>
</tr>
<tr>
<td>Albumin (g/L)</td>
<td>&gt;3.5</td>
<td>15.5</td>
<td>15.5</td>
<td>15.5</td>
<td>15.5</td>
</tr>
<tr>
<td>G-Creatinine (mg/dL)</td>
<td>&lt;2.0</td>
<td>3.7</td>
<td>3.7</td>
<td>3.7</td>
<td>3.7</td>
</tr>
<tr>
<td>Vitamin A (μg/dL)</td>
<td>&gt;38</td>
<td>8.6</td>
<td>8.6</td>
<td>8.6</td>
<td>8.6</td>
</tr>
<tr>
<td>Vitamin C (mg/dL)</td>
<td>&gt;63</td>
<td>8.6</td>
<td>8.6</td>
<td>8.6</td>
<td>8.6</td>
</tr>
<tr>
<td>Total iron (μg/dL)</td>
<td>&gt;100</td>
<td>7.0</td>
<td>7.0</td>
<td>7.0</td>
<td>7.0</td>
</tr>
</tbody>
</table>

ANTIOXIDANTS AND OBESITY

- Absorbed levels of vitamins (serum levels) reduced after weight loss surgery, despite vitamin-mineral supplementation (Donadelli, 2012)
ANTIOXIDANTS AND OBESITY

• Absorbed levels of vitamins (serum levels) reduced after weight loss surgery, despite vitamin-mineral supplementation (Donadelli, 2012)

<table>
<thead>
<tr>
<th>Vitamin</th>
<th>Abnormal %</th>
<th>Total 3 mo</th>
<th>6 mo</th>
<th>12 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>vitamin E</td>
<td>12.8</td>
<td>24.0</td>
<td>14.4</td>
<td>11.8</td>
</tr>
<tr>
<td>vitamin D</td>
<td>7.5</td>
<td>27.5</td>
<td>15.4</td>
<td>11.8</td>
</tr>
<tr>
<td>vitamin A</td>
<td>1.8</td>
<td>8.8</td>
<td>4.3</td>
<td>3.9</td>
</tr>
<tr>
<td>vitamin B6</td>
<td>2.8</td>
<td>13.6</td>
<td>7.8</td>
<td>5.3</td>
</tr>
<tr>
<td>vitamin B12</td>
<td>0.0</td>
<td>1.0</td>
<td>0.7</td>
<td>0.5</td>
</tr>
<tr>
<td>Mean and range</td>
<td>0.0</td>
<td>1.0</td>
<td>0.7</td>
<td>0.5</td>
</tr>
</tbody>
</table>

MICRONUTRIENTS AND SPERM

• Oxidative stress is an important factor in male infertility;
  - Infertile and subfertile men tend to have high levels of reactive oxygen species (ROS);
  - Local antioxidant capacity is suppressed among men with high ROS;
  - Scavenging by local antioxidants could reduce ROS;
  - Increased antioxidants leading to reduced ROS could improve sperm parameters

TRIALS OF ANTIOXIDANTS

• Many study designs are poor
  - Often no control;
  - Failure to measure pre-/baseline values and post-intervention;
  - Difficult to compare due to difference in micronutrient type, dose, timing, and selection of participants

• Among randomized controlled trials, a beneficial effect on motility, concentration, morphology appears

  - Most common antioxidants: vitamin C, E, selenium, zinc, glutathione, L-carnitine, cysteine

OBSERVATIONAL STUDY

• Observational cohort among healthy men observed no association between dietary antioxidant level (beta-carotene, vitamin C, vitamin E, and a composite) on sperm DNA damage (Silver, 2005)

  - DNA Fragmentation Index (DFI) is not outcome of previous studies – no measures of concentration or motility, only specific DNA damage;
  - A previous study from the same group and population noted increases in higher antioxidant intake was associated with higher semen concentration and motility (Eskenazi, 2005);

  - Healthy men

SPECIFIC MICRONUTRIENTS: FATS

• Evidence for an association between fats and semen (Attaman, 2012)

  - Saturated fats: those in highest third had reductions in that sperm count and concentration (p-trend = 0.01)
  - Omega-3 polyunsaturated fats: those in highest third had higher normal morphology than lowest third (p-trend = 0.02)

MICRONUTRIENT CONCLUSIONS

• Obese men after weight loss have been shown to have micronutrient deficiencies, including antioxidants

  - It is unknown how micronutrient level, and the timing of that level, after behavioral lifestyle weight loss intervention may affect sperm characteristics;

  - A biological pathway that includes dietary antioxidants have been associated with sperm concentration and motility in both observational studies and clinical trials
OVERALL CONCLUSIONS

- Excess weight is associated with reduced fertility in men
  - Effect on couples’ infertility is greater when both are overweight or obese
- Weight loss in men has been associated with:
  - Resumption of normalized hormone levels
  - Little-to-no evidence of any effect on semen values
  - No evidence of effect on fertility
- Yet to be measured well:
  - Changes in adipose (total and placement) with weight loss
  - Changes in micronutrients with weight loss