Obesity and Fertility in Women: Can we and should we treat obesity prior to conception?

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Disclosures

- Consultant: Odega, Bayer, Abbvie, Kindex, Fractyl, Millendo, NIH
- Research Funding: Ferring, NIH, Tobacco Settlement Funds PA

Off Label Medications

Sibutramine, Orlistat, Phentermine/Topiramate: Not indicated for infertility
Obese women should lose weight prior to conception as it will clearly improve their chances for pregnancy and a healthy pregnancy.
The most entrenched conflict of interest in medicine is a disinclination to reverse a previous opinion.

Cover Quote, The Lancet, April 9-15, 2011
Conclusions

- Obesity is epidemic in western societies
  - It is associated with reproductive failure (women more than men)
- Obesity alone, however, is only a minor contributor to reproductive failure and pregnancy complications
  - There is no female cutpoint beyond which it is absolutely “unsafe” to have a pregnancy
- Treatments to restore normal weights are largely ineffective in most obese women and may hold reproductive harms not imagined
Disclaimer

- Tonight’s talk is focused solely on reproduction, not long term health.
- The talk is focused on the effects of obesity *per se*, not associated comorbidities.
- What weight is ideal for reproduction might not be applicable for long term health.
- Obesity treatments that improve long term health (diabetes, heart disease, cancer) might not have the same benefits on improving reproduction.
BMI: Body Mass Index

- Weight corrected for height (kg/m$^2$)
BMI: Not always an accurate measure of fat

BMI = 24 kg/m²

BMI = 32 kg/m²
New Zealand: Bronze Medal for World Obesity

1 in 3 New Zealanders are Obese
Women of Reproductive Age are More Likely to be Obese than Men.
Certain Minorities are Disproportionately Affected
Epidemiologic Association of Female Obesity with Reproductive Failure

**Pre-pregnancy**
- Increased time to spontaneous pregnancy
- Increased prevalence of ovulatory dysfunction
  - Polycystic Ovary Syndrome
- Increased Mood Disorders and Diminished Sexual Function

**Pregnancy**
- Increased rate of failure to conceive with treatment
- Increased rates of pregnancy loss (all points of pregnancy)
- Increased rates of major pregnancy morbidities
  - Preterm delivery (infant)
  - Hypertensive Disorders (mother)
- Increased risk of operative delivery and associated morbidity
by Jef Mallett

Benjamin Disraeli said there are three kinds of lies:

Lies, damn lies and statistics.

Nine out of ten people say that was Mark Twain.
<table>
<thead>
<tr>
<th>BMI Group</th>
<th>Adjusted Odds Ratio</th>
<th>95% Confidence Intervals</th>
</tr>
</thead>
<tbody>
<tr>
<td>18.5-25</td>
<td>1.00</td>
<td>Reference</td>
</tr>
<tr>
<td>25-30</td>
<td>1.14</td>
<td>1.07-1.51</td>
</tr>
<tr>
<td>30-35</td>
<td>1.31</td>
<td>1.15-1.36</td>
</tr>
<tr>
<td>35-40</td>
<td>1.37</td>
<td>1.18-1.51</td>
</tr>
<tr>
<td>40-45</td>
<td>1.47</td>
<td>1.14-1.69</td>
</tr>
<tr>
<td>45-50</td>
<td>1.76</td>
<td>1.21-2.31</td>
</tr>
</tbody>
</table>

From SART Registry based on 42,699 IVF cycles
### Risks of Death: U.S. National Safety Council 2008 Data

<table>
<thead>
<tr>
<th>Lifetime risk of death in an automobile accident</th>
<th>1 in 98</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lifetime risk of death in an airplane accident</td>
<td>1 in 7178</td>
</tr>
</tbody>
</table>

Relative Risk (RR) of death in automobile vs airplane: 72.5 (95% CI 5-1151, P = .0024)
## Absolute Chance of IVF Success with Increasing BMI

<table>
<thead>
<tr>
<th>BMI Group</th>
<th>Adjusted Odds Ratio</th>
<th>Chance of Live Birth per IVF cycle</th>
</tr>
</thead>
<tbody>
<tr>
<td>18.5-25</td>
<td>1.00</td>
<td>30%</td>
</tr>
<tr>
<td>25-30</td>
<td>1.14</td>
<td>26%</td>
</tr>
<tr>
<td>30-35</td>
<td>1.31</td>
<td>21%</td>
</tr>
<tr>
<td>35-40</td>
<td>1.37</td>
<td>19%</td>
</tr>
<tr>
<td>40-45</td>
<td>1.47</td>
<td>16%</td>
</tr>
<tr>
<td>45-50</td>
<td>1.76</td>
<td>7%</td>
</tr>
</tbody>
</table>

From SART Registry based on 42,699 IVF cycles and 2014 SART success rates.
How many overweight or obese women do I need to treat to experience one weight-related IVF Failure?

**NNH: Numbers needed to harm**

- 24 for BMI 25-30
- 11 for BMI 30-35
- 9 for BMI 35-40
- 6 for BMI 40-45
- 4 for BMI 45-50
Failure to conceive is not a major public health issue in most developed countries.
Failure to conceive is not a major public health issue in most developed countries.
Failure to conceive is not a major public health issue in most developed countries.

However, doctors may be significantly adding to adverse public health outcomes during pregnancy to mothers and infants, by helping obese women to conceive.
Primum Non Nocere
Hippocratic Oath

First, Do no harm
“Obstetric risks were variably (and mostly marginally) increased as body mass index (BMI) category and obesity class increased.”

N = 148,689 Singleton Pregnancies, 14 centers, 2002-2008
Risk of Maternal Complications by Obesity Class

Kim SS et al, Obstet Gynecol, 2016
Risk of Maternal Complications by Obesity Class

- Maternal ICU admissions NS
  - NS = Not statistically significant for an obesity effect
- Acute Cardiovascular Events

Kim SS et al, Obstet Gynecol, 2016
Relative Risk of Acute Cardiovascular Event

Kim SS et al, Obstet Gynecol, 2016
Risk of Infant Complications by Obesity Class

Preterm Birth (<37 weeks) NS
Early Preterm Birth (<32 weeks)
NICU Admission

NS = Not statistically significant for an obesity effect

Kim SS et al, Obstet Gynecol, 2016
<table>
<thead>
<tr>
<th>Disorder</th>
<th>Number Needed to Harm (NHM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational Hypertension</td>
<td>8</td>
</tr>
<tr>
<td>Infant NICU Admission</td>
<td>18</td>
</tr>
<tr>
<td>Early Preterm Delivery (&lt;32 weeks)</td>
<td>100</td>
</tr>
<tr>
<td>Acute Maternal Cardiovascular Event</td>
<td>333</td>
</tr>
</tbody>
</table>

Kim SS et al, Obstet Gynecol, 2016
### Outcomes

<table>
<thead>
<tr>
<th>Maternal</th>
<th>Infant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational hypertensive disorders</td>
<td>Preterm birth at less than 37 wks of gestation</td>
</tr>
<tr>
<td>Gestational diabetes</td>
<td>Early preterm birth at less than 32 wks of gestation</td>
</tr>
<tr>
<td>Placental previa</td>
<td>Late preterm birth at 32 to less than 37 wks of gestation</td>
</tr>
<tr>
<td>Cesarean delivery</td>
<td>Stillbirth</td>
</tr>
<tr>
<td>Prelabor cesarean delivery</td>
<td>LGA</td>
</tr>
<tr>
<td>Intrapartum cesarean delivery</td>
<td>Birth injury</td>
</tr>
<tr>
<td>Cesarean delivery after induction</td>
<td>Congenital anomaly</td>
</tr>
<tr>
<td>Cesarean delivery after spontaneous labor</td>
<td>Transient tachypnea</td>
</tr>
<tr>
<td>Operative vaginal delivery</td>
<td>Apnea</td>
</tr>
<tr>
<td>Induction</td>
<td>Aspiration</td>
</tr>
<tr>
<td>Oxytocin augmentation</td>
<td>Asphyxia</td>
</tr>
<tr>
<td>Abruptio</td>
<td>Sepsis</td>
</tr>
<tr>
<td>3rd- or 4th-degree laceration</td>
<td>Seizure</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>Intracranial hemorrhage</td>
</tr>
<tr>
<td>Blood transfusion</td>
<td>NICU admission</td>
</tr>
<tr>
<td>Maternal fever</td>
<td>Among preterm births</td>
</tr>
<tr>
<td>Major puerperal infection</td>
<td>Respiratory distress syndrome</td>
</tr>
<tr>
<td>Infection of genitourinary tract</td>
<td>Necrotizing enterocolitis</td>
</tr>
<tr>
<td>Complication of surgical wounds</td>
<td>PVH-IVH</td>
</tr>
<tr>
<td>Hysterectomy</td>
<td>Retinopathy of prematurity</td>
</tr>
<tr>
<td>Acute cardiovascular events</td>
<td></td>
</tr>
<tr>
<td>Maternal ICU admission</td>
<td></td>
</tr>
</tbody>
</table>

*Kim SS et al, Obstet Gynecol, 2016*

Kim SS et al, Obstet Gynecol, 2016
<table>
<thead>
<tr>
<th>BMI Group</th>
<th>Adjusted Relative Risk</th>
<th>95% CI</th>
<th>Number Needed to Harm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal BMI</td>
<td>1.00</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Overweight</td>
<td>1.05</td>
<td>1.05-1.06</td>
<td>27</td>
</tr>
<tr>
<td>30-35</td>
<td>1.07</td>
<td>1.07-1.08</td>
<td>20</td>
</tr>
<tr>
<td>35-40</td>
<td>1.09</td>
<td>1.08-1.10</td>
<td>16</td>
</tr>
<tr>
<td>&gt;40</td>
<td>1.12</td>
<td>1.11-1.13</td>
<td>11</td>
</tr>
</tbody>
</table>

Kim SS et al, Obstet Gynecol, 2016
Obesity and Female Reproduction

- Obesity is associated with increased risk for reproductive failure and maternal and infant morbidity
  - Not every morbidity is increased
  - Normal weight women have high baseline rates for similar morbidities
- However, the risk, when present with obesity, tends to be linear and marginal
  - Even for the highest weight classes
Conclusion: “While the overall quality of the studies included in this review was poor… (only 2 RCTs, not powered for live birth)”
## Small Studies Favor Lifestyle Intervention Improving Fertility

<table>
<thead>
<tr>
<th>Reference, Year</th>
<th>N</th>
<th>Intervention</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Becker GF et al, Am J Clin Nutr, 2015</td>
<td>26</td>
<td>Hypocaloric/ Low glycemic index diet vs control x 12 weeks</td>
<td>3 live births in diet arm</td>
</tr>
<tr>
<td>Sims KA and et al, Clin Obesity 2014</td>
<td>59</td>
<td>Varying Low Calorie Diet/Group intervention vs Usual Care x 12 weeks</td>
<td>Live Birth Rate: 44% in diet vs 14% in Usual Care</td>
</tr>
</tbody>
</table>
Why Most Published Research Findings Are False

John P. A. Ioannidis

- Study is small
- Greater number and lesser pre-selection of tested relationships
- Greater flexibility in design, definitions, outcomes, and analyses

Randomized Trial of a Lifestyle Program in Obese Infertile Women

Meike A.Q. Mutsaerts, M.D., Ph.D., Anne M. van Oers, M.D.,

577 Were randomly assigned to treatment

290 Were assigned to 6 mo of lifestyle intervention before 18 mo of infertility treatment

287 Were assigned to prompt 24 mo of infertility treatment
The Diabetes Prevention Program

A Randomized Clinical Trial to Prevent Type 2 Diabetes in Persons at High Risk: Lifestyle Modification VS Metformin VS Placebo Control

The DPP Research Group
Lifestyle Intervention-Diabetes Prevention Program

An intensive program with the following specific goals:

• ≥ 7% loss of body weight and maintenance of weight loss
  – Dietary fat goal -- <25% of calories from fat
  – Calorie intake goal -- 1200-1800 kcal/day

• ≥ 150 minutes per week of physical activity
The DPP Research Group, *NEJM* 346:393-403, 2002

The graph illustrates the mean weight change (kg) over years from randomization for Placebo, Metformin, and Lifestyle interventions. The y-axis represents weight change in kilograms, ranging from -8 to 0, while the x-axis shows years from randomization, from 0 to 4 years. Each intervention shows a distinct trend in weight change over time.
**Incidence of Diabetes**

- Placebo (n=1082)
- Metformin (n=1073, p<0.001 vs. Placebo)
- Lifestyle (n=1079, p<0.001 vs. Metformin, p<0.001 vs. Placebo)

**Risk reduction**
- 31% by metformin
- 58% by lifestyle

The DPP Research Group, *NEJM* 346:393-403, 2002
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Mean Starting Weight ~ 100kg

Lost 4.4 kg

Lost 1.1 kg
CONCLUSIONS

In obese infertile women, a lifestyle intervention preceding infertility treatment, as compared with prompt infertility treatment, did not result in higher rates of a vaginal birth of a healthy singleton at term within 24 months after randomization. (Funded by the Netherlands Organization for Health Research and Development; Netherlands Trial

Mutsaerts et al, NEJM, 2016
No Significant Differences in Pregnancy Complications Between Groups, but..

<table>
<thead>
<tr>
<th>Complication</th>
<th>Intervention</th>
<th>Control</th>
<th>Rate Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy Loss</td>
<td>14.6 %</td>
<td>9.5 %</td>
<td>1.54 (0.98-2.43)</td>
</tr>
</tbody>
</table>

Mutsaerts et al, NEJM, 2016
Are there subsets of infertile women who may benefit from weight loss

Is there a dose response relationship, i.e. the more the weight loss the better the fertility response
Polycystic Ovary Syndrome

- A syndrome of excess androgen, chronic anovulation and polycystic ovaries
- The leading female cause of infertility in the U.S.
- Often associated with obesity
  - Weight loss is thought to improve ovulation and fertility
Infertile Overweight/Obese Women with PCOS N = 149

Lifestyle Modification

Continuous OCP

Combined

16 Weeks

Ovulation Induction with Clomiphene: 4 cycles

Conception: Follow q trimester

PRIMARY OUTCOME: Live Birth

Clinicaltrials.gov: NCT00704912

Legro et al, JCEM, 2015
Lifestyle Modification with Weight Loss (7% Target)

- **Meal Replacements** for all 3 meals with fresh vegetables/fruit supplement (Caloric Restriction) – 500kcal/day Deficit

- **Increased Physical Activity** (Target: 150 mins/wk)

- **Brief Behavioral Modification Lessons** (Monthly) – Adapted from the Diabetes Prevention Program

- **Weight loss medication** (BMI ≥ 30 only)
  - Sibutramine 5-15 mg/d
  - After the FDA Sibutramine Advisory in 2010 we used over the counter orlistat (60 mg) TID with meals
Percent Weight Loss After Preconception Intervention of 16 Weeks

* P < .0001

No difference between weight loss with sibutramine or orlistat
Kaplan Meier Curve: Live Birth Primary Outcome

Legro et al, JCEM, 2015
Post Hoc Analysis: Combination of Lifestyle and Combined into One Treatment Group

Legro et al, JCEM, 2015
Effects of Preconception Weight Loss in Obese Women with PCOS vs Immediate Infertility Treatment

- Women were more likely to ovulate with treatment after weight loss (RR 1.4 95% CI 1.1-3.2)
- Women were more fecund, i.e. more likely to have a baby if they ovulated after weight loss than if they were treated immediately without weight loss (RR 2.5 95% CI 1.4-4.6).

Legro et al, JCEM, 206
Morbid Obesity is Associated with the Highest Risk for Infertility and Adverse Pregnancy Outcomes

Therefore they should benefit the most from massive weight loss
Followed 29 obese reproductive aged women (off confounding reproductive/metabolic medications) from pre-op (mean weight 132 kg and BMI 49) to 24 months post Roux-en-Y Gastric Bypass
No Change in Ovulation Rate Despite Significant Weight Loss after Surgery

* P < .01 vs Baseline

Legro et al, JCEM, 2012
Weight Loss has no Effect on the Quality of Ovulation

Legro et al, JCEM, 2012
More than 50% of women reported “irregular menses” at baseline.
# Improved Sexual Function After Bariatric Surgery

<table>
<thead>
<tr>
<th>Sexual Function</th>
<th>Visit 1 (1mo pre-surgery)</th>
<th>Visit 5 (12mo post-surgery)</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD) [n]</td>
<td>Mean (SD) [n]</td>
<td></td>
</tr>
<tr>
<td>Female Sexual Function Index Total Score</td>
<td>16.3 (8.7) [14]</td>
<td>24.6 (6.8) [17]</td>
<td>0.007</td>
</tr>
</tbody>
</table>

Legro et al, JCEM 2012
They identified 627,693 singleton pregnancies in the Swedish Medical Birth Registry, 670 after bariatric surgery: Used a 5 obese control to 1 case analysis

**CONCLUSIONS**

Bariatric surgery was associated with reduced risks of gestational diabetes and excessive fetal growth, shorter gestation, an increased risk of small-for-gestational-age infants, and possibly increased mortality. (Funded by the Swedish Research Council and others.)
Increased Risk of Fetal/Neonatal Mortality after Bariatric Surgery

● The risk of stillbirth or neonatal death was 1.7% versus 0.7% (odds ratio, 2.39; 95% CI, 0.98 to 5.85; P=0.06).

● There was no significant between-group difference in the frequency of congenital malformations.

Odds ratios for gestational diabetes and adverse perinatal outcomes according to change in BMI in the bariatric surgery cohort versus the control cohort

<table>
<thead>
<tr>
<th>Subgroup and BMI Units</th>
<th>Bariatric-Surgery Cohort</th>
<th>Control Cohort</th>
<th>Odds Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational diabetes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;12.9</td>
<td>4/253 (1.6)</td>
<td>71/1141 (6.2)</td>
<td></td>
<td>0.67</td>
</tr>
<tr>
<td>≥12.9</td>
<td>7/306 (2.3)</td>
<td>80/1088 (7.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LGA</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&lt;12.9</td>
<td>37/263 (14.1)</td>
<td>226/1157 (19.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥12.9</td>
<td>12/309 (3.9)</td>
<td>276/1112 (24.8)</td>
<td></td>
<td></td>
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<tr>
<td>SGA</td>
<td></td>
<td></td>
<td></td>
<td>0.52</td>
</tr>
<tr>
<td>&lt;12.9</td>
<td>40/263 (15.2)</td>
<td>88/1157 (7.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥12.9</td>
<td>52/309 (16.8)</td>
<td>87/1112 (7.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preterm birth</td>
<td></td>
<td></td>
<td></td>
<td>0.04</td>
</tr>
<tr>
<td>&lt;12.9</td>
<td>20/263 (7.6)</td>
<td>94/1163 (8.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥12.9</td>
<td>37/309 (12.0)</td>
<td>74/1114 (6.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malformations</td>
<td></td>
<td></td>
<td></td>
<td>0.08</td>
</tr>
<tr>
<td>&lt;12.9</td>
<td>3/263 (1.1)</td>
<td>44/1163 (3.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥12.9</td>
<td>10/309 (3.2)</td>
<td>35/1114 (3.1)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Women who lost the most weight after bariatric surgery were at greater risk for small babies and preterm birth than obese women without treatment!!

<table>
<thead>
<tr>
<th></th>
<th>LGA</th>
<th>SGA</th>
<th>Preterm birth</th>
<th>Malformations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;12.9</td>
<td>≥12.9</td>
<td>&lt;12.9</td>
<td>&lt;12.9</td>
</tr>
<tr>
<td></td>
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<td>12/309 (3.9)</td>
<td>40/263 (15.2)</td>
<td>3/263 (1.1)</td>
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</tr>
</tbody>
</table>

The mechanism behind improved fecundity with bariatric surgery may involve improved sexual function, not change in ovulatory function.

There is an increased risk for small babies and preterm labor in obese women who undergo bariatric surgery compared to those who don’t.

- May increase with more weight lost
- Concerning trend towards increased infant mortality
Is there an upper limit of weight beyond which there is no hope of return to a normal weight?
## Best Estimates of Weight Loss at 12 mos of Treatment among Compliant Patients

<table>
<thead>
<tr>
<th>BMI Category</th>
<th>Type of Weight loss</th>
<th>Specific Intervention</th>
<th>Amount of weight loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-34.9</td>
<td>Lifestyle</td>
<td>Diabetes Prevention Program</td>
<td>7%</td>
</tr>
<tr>
<td>35-35.9</td>
<td>Medication</td>
<td>Phentermine/Topiramate (Qysmia in U.S.)</td>
<td>15%</td>
</tr>
<tr>
<td>≥ 40</td>
<td>Bariatric Surgery</td>
<td>Swedish Obesity Study (Roux-en-Y Gastric Bypass)</td>
<td>45%</td>
</tr>
</tbody>
</table>
Best Results of Weight Loss at 12 months of Treatment

BMI after 12 mos

Proposed BMI Cutoff

Obesity Cutoff

Baseline BMI

Lifestyle
Weight Loss Drug
Bariatric Surgery

BMI

0 10 20 30 40 50 60

35 40 45 50 55 60

Baseline BMI
Factors Associated With Achieving a Body Mass Index of Less Than 30 After Bariatric Surgery

- Patients with a preoperative BMI of less than 40 are more likely to achieve a BMI of less than 30 after bariatric surgery (odds ratio [OR], 12.88; 95% CI, 11.71-14.16) and are more likely to experience comorbidity (diabetes, hypertension, lipid abnormalities) remission.

- Patients with a BMI ≥ 50 have only a 8.5% chance of obtaining a BMI less than 30 after bariatric surgery.

- Policies and practice patterns that delay bariatric surgery until the BMI is 50 or greater can result in significantly inferior outcomes.

Varban et al, JAMA Surgery 2017
Why is it so difficult for humans to lose weight?

Why is it more difficult to women to lose weight than men?
Fat and Female Reproduction

- Fat is essential to female reproductive maturation and for the maintenance of ovulation and ultimately for early pregnancy.
- Women have larger percentages of body fat at all life stages than men.
- Women lose fat at a slower rate than men when challenged with the same treatment.
Body Fat Composition in U.S. Men and Women

National Health and Nutrition Examination Survey, United States, 1999--2004
Menarche (First Menses) is dependent on a critical fat mass

Mean weight at Menarche 47 kg

The age of menarche has fallen in the developed world over the last 150 years due to improved nutrition and increasing childhood obesity rates.

Frisch RE, Science, 1974
Body Fat % Unchanged During Perimenarche

Legro et al, JCEM, 2000
Fat Requirement for Female Reproduction

- Lower Limit
- No ovulation
- No Upper Limit to Fat

Anorexia Nervosa
Gymnasts
Marathon Runners
When Leptin levels fall due to decreased fat mass, leptin circulates directly proportional to the amount of fat. This leptin stimulates the hypothalamus, leading to increased food intake and energy expenditure, which in turn helps increase fat mass.
1. Fat cells empty
2. No leptin signal
3. We eat

4. Fat cells full
5. Leptin signal
6. We stop eating
Restoration of Normal Reproductive Hormone Levels in Thin Women Who Ovulated during Recombinant Leptin Treatment

Leptin Resistance

1. Fat cells empty
2. No leptin signal
3. We eat

4. Fat cells full
5. Leptin signal
6. We stop eating
Hypothalamus and Obesity

- The Hypothalamus resets “normal” weight to the highest weight obtained and attempts to maintain that weight (fat mass) at all costs
- Leptin levels are high in obese patients
  - Giving them recombinant leptin does not result in significant weight loss due to leptin resistance
- There are multiple redundant neural and hormonal pathways to restore weight
  - There are multiple hormones to stimulate appetite
The Hypothalamus is Shallow Hal when it comes to Obesity
One year after initial diet-induced weight reduction, levels of the circulating hormones of appetite that encourage weight regain after diet-induced weight loss do not revert to the levels recorded before weight loss.
Hunger and Desire to Eat are maintained after weight loss for a prolonged period (one year) even with weight maintenance after the weight loss intervention.
Effect of Energy Deficit (500kcal/day) and Vigorous Exercise on Bodyweight

Hall KD, Lancet 2011

Will obese women with infertility wait 3-4 years to achieve steady state weight?

Vigorous Exercise only adds 2-3% additional weight loss
Weight Loss during 30 days of starvation among Men and Women

“The therapeutic regimen consisted simply of no food”

Runcie and Hilditch, BMJ, 1974
Excessive weight loss through severe calorie restriction rarely results in long term weight maintenance and may have added reproductive toxicity in women.
Effect of a very-low-calorie diet on in vitro fertilization outcomes

A low-calorie diet in a group of overweight or obese patients for a short period before and during IVF results in variable tolerance to the dietary regime and an unsatisfactory IVF outcome. (Fertil Steril® 2006;86:227–9. ©2006 by American Society for Reproductive Medicine.)

- ~500kcal/d diet
- Lost 2.2-8.8% of body weight in a 4-6 week period
- Poor oocyte number, quality, and fertilization
- Intervention stopped after 10 patients

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Limitations of Weight Loss in Obese Women with Infertility

● Dose?
  ◆ Is there an ideal rate of weight loss or activity increase

● Duration?
  ◆ How long should the intervention be instituted

● Timing?
  ◆ Is the intervention before or during infertility treatment or both?

● Patient Compliance?
  ◆ Will patients elect to participate
  ◆ Will they be able to follow our recommendations
  ◆ How can we as clinicians ensure compliance
Conclusions

- Obesity is epidemic in western societies
  - It is associated with reproductive failure (women more than men)
- Obesity alone, however, is only a minor contributor to reproductive failure and pregnancy complications
  - There is no female cutpoint beyond which it is absolutely “unsafe” to have a pregnancy
- Treatments to restore normal weights are largely ineffective in most obese women and may hold reproductive harms not imagined
Obese women should be told that weight loss prior to conception *MAY* result in minor improvements in pregnancy and pregnancy complication rates.

Delay in infertility therapy to lose weight *MAY* result in a decreased chance for pregnancy.

There may be an upper limit of baseline weight which *MAY NOT* benefit (even modestly) from weight loss.
WE HAVE MET THE ENEMY AND HE IS US.
OWL-PCOS: QCP vs Weight Loss for Pregnancy in Polycystic Ovary Syndrome (R01HD056510)
Steering Committee of the PPCOS II Trial
Thank you Patient Participants!
Sexually Dimorphic Reproductive Effects in Men and Women

Women
- Early Puberty
- Excess ovarian function with higher androgen levels
- Breast Shrinkage

Men
- Delayed puberty
- Decreased testicular function with higher estrogen levels
- Breast Development
Mechanisms of Hypogonadism in Obese Males or Hypergonadism in Women

Schneider G, JCEM, 1979
Combination Therapy (Lifestyle/Medication/Behavior) Achieves Best Weight Loss

Weight loss Plateaus between 10-18 weeks

Average weight change during a 30d fast in Obese Men (N = 18) or Women (N = 58)

Adapted from Runcie and Hilditch BMJ, 1974
Summary: Lifestyle Lessons Learned

- Most patients will not even attempt a lifestyle intervention if it is offered to them.
- Many who do will drop out.
  - 50% dropout rates in 3-6 month studies.
- Severely obese patients may be poor candidates for such programs which focus on activity.
  - Focus on diet, given difficulty with weight-bearing exercise.
Modest Effects, long time required, much less weight loss than we promise
  – Counterregulatory effects diminish caloric restriction effects
  – Thinner people require fewer calories

There will be hurdles to implementing these programs in our current U.S. medical system
Conclusions: Clinical Care

- Preconception lifestyle modification in overweight/obese women with PCOS improves ovulation rates with clomiphene vs pretreatment with OCP
  - Treatment is relatively simple, safe and well tolerated.
- OCP pretreatment likely offers little benefit versus immediate treatment with ovulation induction.
- Concurrent Lifestyle Modification should be recommended for overweight/obese women with PCOS on OCP therapy.
  - Eliminates adverse metabolic effects of OCP
...and now, a word from our Sponsors...
Modeling of Projected Weight Loss with Longer Interventions
Weight will Rebound during Infertility Treatment and Pregnancy
Obese Women (BMI ≥30 and Age ≤ 40y) with Unexplained Infertility (N = 380)

**Intensive Lifestyle Modification:**
Weight Loss AND Increased Physical Activity (N = 190)

**Standard Lifestyle Modification:**
Increased Physical Activity (N = 190)

3 cycles of Ovarian Stimulation with Clomiphene /Insemination (Clamp physical activity and weight during this phase)

Pregnancy (3 visits): One per trimester for weight, blood pressure, and glycemic measures

**Primary Outcome:** Good Birth Outcome: Healthy singleton or twin Live Birth (≥ 37 weeks, 2500-4000g, no major anomaly)

Infant Follow up