Management Of Obesity as an Endocrine Disease: Implications for Guidelines

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Objectives

• Examine the role of endocrine systems in obesity pathophysiology
• Understand how weight loss can help ameliorate the endocrine and metabolic abnormalities that that are integral to the disease process
• Understand how the interaction between excess adiposity and abnormal endocrine and metabolic functioning can inform guidelines and provide rationale for therapeutic approaches

1. PATHOPHYSIOLOGY:
   • Enteroendocrine – hypothalamic axis
2. WEIGHT LOSS AND ENDOCRINE DISEASE:
   • Infertility and PCOS
   • Adipose tissue dysfunction and cardiometabolic disease
3. APPLICATION OF AACE OBESITY GUIDELINES:
   • Patient-centered weight loss therapy for endocrine disease
ROLE OF THE ENTEROENDOCRINE AXIS

• Positive energy balance and the promotion of excess adiposity
• Protection of excess adiposity in the face of weight loss interventions

Regulation of Energy Intake

Courtesy of Dr. W. Timothy Garvey, 2013.
In Obesity, biology protects against weight loss and maintains a high body weight

- ↑ Ghrelin
- ↓ Leptin, PYY, CCK, Amylin
- ↓ Resting energy expenditure
- ↑ Hunger
- ↑ Calorie-dense food preferences

Equilibrium Weight
Baseline weight 250 lbs

Weight Loss
Weight Gain

Increased Appetite
Decreased Energy Out
Increased Energy In

Garvey WT, 2014

Adaptations to Weight Loss: Obesity Protects Obesity

Orexigenic Hormones ↑
- Ghrelin

Anorexigenic Hormones ↓
- Leptin, PYY, CCK, GLP-1, amylin, insulin

Eating Behavior
- ↑ Hunger, Prefer calorie dense foods

Metabolism
- ↓ Fat oxidation
- ↑ Cortisol

Nervous System
- ↓ SNS activity, FNI: increased mesolimbic reward center

Energy Expenditure
- ↓ TEE, ↓ REE, ↓ NREE, ↓ T4

Energy intake
Body Weight
Energy expenditure

## Enteroendocrine Cell Subsets Controlling Appetite

<table>
<thead>
<tr>
<th>EEC Type</th>
<th>Hormone</th>
<th>Location</th>
<th>Effect</th>
<th>Luminal Receptors</th>
<th>Stimuli</th>
</tr>
</thead>
<tbody>
<tr>
<td>P/D1-Like Cells</td>
<td>Ghrelin</td>
<td>Stomach</td>
<td>↑ Food intake</td>
<td>T1R1-T1R3, T2Rs</td>
<td>Carbs, LCFA</td>
</tr>
<tr>
<td></td>
<td>Obestatin</td>
<td></td>
<td>↓ Food intake</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nesfatin-1</td>
<td></td>
<td>↓ Food intake</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>↑ Insulin secretion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I Cells</td>
<td>CCK</td>
<td>Proximal intestine</td>
<td>↑ Food intake</td>
<td>T2Rs, α-Gustducin, FFA1, CaSR</td>
<td>Carbs, amino acids</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>↑ GB contraction/pancreas</td>
<td></td>
<td></td>
</tr>
<tr>
<td>K Cells</td>
<td>GIP</td>
<td>Proximal intestine</td>
<td>↑ Insulin secretion</td>
<td>GRP120, GRP119, SGLT1, α-Gustducin</td>
<td>Carbs, FAs, amino acids</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>↑ Gastric emptying</td>
<td></td>
<td></td>
</tr>
<tr>
<td>L Cells</td>
<td>GLP-1</td>
<td>Distal small and large intestine</td>
<td>↑ Food intake</td>
<td>T1R2/T1R3, T2Rs, GPR120, LPAR5</td>
<td>Carbs, MCFA/LCFA, exercise</td>
</tr>
<tr>
<td></td>
<td>GLP-2</td>
<td></td>
<td>↑ Insulin secretion</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>↑ GI motility</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>↑ Glucagon</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Glicentin</td>
<td></td>
<td>↑ Mucosal growth</td>
<td>GPR131 (TGR5)</td>
<td>Bile acids</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>↑ Gastric emptying</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>PYY</td>
<td></td>
<td>↓ Food intake</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>↓ GI motility</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Oxynto-modulin</td>
<td></td>
<td>↑ Weight loss</td>
<td>GPR119</td>
<td>Lipids</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>↑ Energy expenditure</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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Post-translational Processing of Preproglucagon
Multiple sensors and multiple downstream effectors of gut sensory systems, using the L cell as an example


Role of enteroendocrine cells in substrate metabolism and energy balance

Spreckley E & Murphy KG. Frontiers Nutr. 2015
PYY Levels 90 Minutes After Test Meals are Reduced in Obesity

Le Roux CW et al. Endocrinol 2006; 147:3-8

Post-Prandial GLP-1 Levels are Suppressed in Patients with Obesity

Ghrelin Levels Remain Elevated Following a Meal in Patients with Obesity

Fasting and Postprandial Levels of Ghrelin, Peptide YY, Amylin, and Cholecystokinin (CCK) at Baseline, 10 Weeks, and 62 Weeks of Weight Loss


Fasting and Postprandial Ratings of Hunger and Desire to Eat at Baseline, 10 Weeks, and 62 Weeks.


24-Hour Plasma Ghrelin Profiles in 13 Obese Subjects before and after Diet-Induced Weight Loss

The Pathophysiology of Obesity: Why do patients so frequently regain weight following lifestyle therapy

It is difficult for patients to maintain their weight loss over time.

Sacks FS. et al. NEJM 2009;360(9) 859-873.
Actions of Recently Approved Weight-Loss Medications

Arcuate Nucleus

Paraventricular Nucleus

Liraglutide 3 mg

MC4R

GABA?

Topiramate

Dopamine/NE reuptake

Higher Cortical Centers

Decreased Appetite

Phentermine

GLP-1 R

POMC/CART

Lorcaserin

μ-OR

Naltrexone

Serotonergic Neurons

α-MSH

S-HT2c

Topiramate

Bupropion

Phentermine

GLP-1 R

POMC/CART

Lorcaserin

μ-OR

Naltrexone

Serotonergic Neurons

α-MSH

S-HT2c

Topiramate

Bupropion

MC4R, melanocortin 4 receptor.
GABA, gamma-aminobutyric acid.
POMC/CART, pro-opiomelanocortin/cocaine- and-amphetamine-regulated transcript.

Courtesy of Dr. W. Timothy Garvey, 2014.

Summary

• It is difficult for patients to maintain weight loss. — Obesity protects obesity
• They are fighting pathophysiological mechanisms that are primal to the disease of obesity.
• Body weight is not a cognitive function.
• Patients need our help:
  • evidenced based approaches to medical care;
  • comprehensive, structured, individualized, lifestyle therapy programs;
  • medications that counteract pathophysiology;
  • health care professionals that get it.
WEIGHT LOSS AND ENDOCRINE DISEASE

1. Adipose tissue dysfunction and cardiometabolic disease
2. Infertility and PCOS
The image contains a flowchart that outlines the process of managing and treating obesity. It includes sections for Patient Presentation, Diagnosis, Clinical Diagnosis, Diagnostic Categories, and Phases of Chronic Disease Prevention and Treatment Goals. The chart categorizes patients based on their BMI (Body Mass Index) and outlines stages of obesity, including normal weight, overweight (BMI 25-29.9), and obesity (BMI ≥30). It also details the phases of chronic disease prevention and treatment, with primary, secondary, and tertiary approaches. The follow-up section highlights the importance of ongoing evaluation and treatment adjustments. The chart is designed to guide healthcare providers through the process of assessing and managing obesity-related conditions.
The Spectrum of Cardiometabolic Disease

Prediabetic States
1. Prediabetes
   i. IFG
   ii. IGT
2. Metabolic Syndrome
   • Waist
   • blood pressure
   • fasting glucose
   • Triglycerides
   • HDL-cholesterol

Type 2 Diabetes

Cardiovascular Disease

Increased Waist Circumference and Risk of Diabetes and CVD


Relationship Between Visceral Adipose Tissue and Insulin Action


Inflammatory Macrophage Infiltration in Adipose Tissue in Obesity

Sun K et al. JCI 121:2094-2101, 2011
Macrophage Infiltration and Crown-Like Structures in Adipose Tissue from Patients with Metabolic Syndrome

Bremer AA et al. JCEM 96:E1782-E1788, 2011

Bastard JP et al. Eur Cytokine Network 17:4-12, 2006
Macrophage infiltration of scWAT in obese subjects before (T0) and 3 months after (3M) weight loss surgery.


Association between weight loss (%) and change in adipokines.

Effects of Short-term VLCD on Body Fat and Insulin Sensitivity

Baseline  Post-VLCD

<table>
<thead>
<tr>
<th>Body Weight (kg)</th>
<th>Fat Mass (kg)</th>
<th>GDR (per LBM)</th>
<th>IMCL</th>
</tr>
</thead>
<tbody>
<tr>
<td>120</td>
<td>55</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>110</td>
<td>45</td>
<td>9</td>
<td>4</td>
</tr>
<tr>
<td>100</td>
<td>35</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>90</td>
<td>25</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>80</td>
<td>15</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>70</td>
<td>5</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>60</td>
<td>4</td>
<td>4</td>
<td>9</td>
</tr>
<tr>
<td>50</td>
<td>3</td>
<td>3</td>
<td>10</td>
</tr>
</tbody>
</table>

P < 0.001  P = 0.083  P < 0.05  P < 0.02


Metabolic Syndrome
Adiponectin as a Paradigm for Pathophysiology

Dysfunctional Fat

↓ Adiponectin

Metabolic
Insulin Resistance, Metabolic Syndrome, T2DM

Vascular
Atherosclerosis, CVD events
Epidemiology of Adiponectin

Low levels are associated with
- Type 2 Diabetes
- Obesity
- Insulin Resistance
- Metabolic Syndrome
- Cardiovascular Disease

High Levels associated with
- Lean
- Cardiometabolic Wellness

Adiponectin Multimers and Insulin Sensitivity

Adiponectin Hyperexpression Augments Adipocyte Recruitment and Differentiation

Adiponectin Hypersecretion Enhances Insulin-Stimulated Glucose Transport in 3T3-L1 Adipocytes

Fu, Luo, Klein, Garvey, JLR, 2005
Cell Model

Human THP-1 monocytes

PMA: phorbol 12-myristate 13-acetate
oxLDL: oxidized low-density lipid
Adiponectin

Fatty Streak
Foam Cells

Macrophages

PMA 24hr
Rest 24hr

oxLDL 24hr
Adiponectin decreases lipid accumulation in macrophage foam cells

Red Oil O staining of macrophage foam cells analyzed by NIH ImageJ software. *p<0.01

AdipoR1 Hyperexpression in Macrophages Improves Glucose Tolerance and Insulin Sensitivity

Liver Weight and Fat Content are Reduced in Macrophage AdipoR1 Transgenic Mice when Fed High Fat Diets

![Liver Weight chart](chart.png)

Oilo Red O stain of Liver in High Fat Fed Mice


Macrophage AdipoR1 Affects Atherosclerosis

![Macrophage AdipoR1 Atherosclerosis chart](chart2.png)

Metabolic Syndrome
Adiponectin as a Paradigm for Pathophysiology

Dysfunctional Fat

↓ Adiponectin

Macrophage

Metabolic
Insulin Resistance, Metabolic Syndrome, T2DM

Vascular
Atherosclerosis, CVD events

Incident Diabetes During the DPP

All Participants

- Placebo (n=1082)
- Metformin (n=1073)
- Lifestyle (n=1079)

Risk reduction
31% by metformin
58% by lifestyle

Effect of Phentermine/Topiramate ER on Weight Loss in Obese Adults Over 2 Years: SEQUEL Study

![Graph showing weight loss over weeks for different treatment groups.]


Effect of Weight Loss Induced by Phentermine/Topiramate ER on the Prevention of Diabetes in Patients With Metabolic Syndrome and/or Prediabetes: SEQUEL Study

![Graph showing cumulative incidence rate of type 2 diabetes over weeks for different treatment groups.]

**Cardiometabolic Disease Staging (CMDS)**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Criteria</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No Risk Factors</td>
<td>Healthy Obese ¹</td>
</tr>
<tr>
<td>1</td>
<td>1 or 2 Risk Factors (waist, blood pressure, triglycerides, HDL-c)</td>
<td>Metabolic Syndrome has low sensitivity for CMD, and 1 or 2 risk factors elevates risk of future T2DM and CVD ²,³</td>
</tr>
<tr>
<td>2</td>
<td>Metabolic Syndrome OR Prediabetes (i) Metabolic Syndrome alone, OR (ii) IFG, OR (iii) IGT</td>
<td>Both Metabolic Syndrome and Prediabetes confer increased risk of T2DM and CVD ³,⁴</td>
</tr>
<tr>
<td>3</td>
<td>Metabolic Syndrome PLUS Prediabetes 2 or more out of 3: Metabolic Syndrome, IFG, IGT</td>
<td>Risk of future T2DM is double in patients with both Metabolic Syndrome and Prediabetes compared with either alone ³-⁶</td>
</tr>
<tr>
<td>4</td>
<td>End-Stage Cardiometabolic Disease Type 2 Diabetes and/or CVD</td>
<td>T2DM is CVD risk equivalent ⁷</td>
</tr>
</tbody>
</table>

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**Cumulative Diabetes Incidence as a Function of Increasing CMDS Risk Stage: CARDIA Study Cohort**

![Graph showing cumulative diabetes incidence as a function of follow-up time](image)

Guo F, Moellering DR, Garvey WT. Obesity 22:110, 2014
### Weighting of Factors Conferring Risk of Diabetes in the CARDIA Study Cohort: The Weighted CMDS Score

<table>
<thead>
<tr>
<th>Items</th>
<th>CMDS Score</th>
<th>Modified CMDS Score*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fasting glucose</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• IFG, ≥100 mg/dL</td>
<td>23</td>
<td>30</td>
</tr>
<tr>
<td><strong>2-hour glucose</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• IGT, ≥140 mg/dL</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td><strong>Waist circumference</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• ≥102 cm in men, ≥88 cm in women</td>
<td>26</td>
<td>33</td>
</tr>
<tr>
<td><strong>Blood pressure</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• systolic ≥130 and/or diastolic ≥85 mmHg</td>
<td>20</td>
<td>22</td>
</tr>
<tr>
<td>• or on anti-hypertensive medication</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>HDL cholesterol</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• &lt;40 mg/dL in men; &lt;50 mg/dL in women</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td><strong>Fasting triglycerides</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• ≥150 mg/dL or on lipid lowering medication</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td><strong>Total (range 0 to 100)</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Modified CMDS score eliminates 2-hour glucose

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**Weighted CMDS Predicts 15 Year Risk of Diabetes in the CARDIA Study Cohort**

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Guo F, Garvey WT. JCEM, 100:3871, 2015

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Guo F, Garvey WT. JCEM, 100:3871, 2015
Incident T2DM in the ARIC Study
Lean, Overweight, and Obese Subjects who were either metabolically healthy or had the Metabolic Syndrome

CONCLUSIONS: 1. BMI has relatively small impact on T2DM risk in insulin sensitive individuals.
2. BMI has larger impact on T2DM risk in insulin resistant individuals

Manuscript submitted

Domenic M. Rubino, MD.
WEIGHT LOSS AND ENDOCRINE DISEASE

1. Adipose tissue dysfunction and cardiometabolic disease
2. Infertility and PCOS
Sex Hormone Disorders Associated with Obesity and Insulin Resistance

**PCOS in Women**

**Disease features**
- Anovulation or irregular menstrual cycles with hyperandrogenism
- Pathophysiologically linked to insulin resistance
- Increased risk for T2DM, dyslipidemia, hypertension, inflammation, and CVD

**Treatment**
- Increase insulin sensitivity
  - Aerobic exercise and weight loss
  - Metformin* or pioglitazone†
- Spironolactone or other nonandrogenic oral contraceptive for skin manifestations (hirsutism, acne)

*Not FDA approved for PCOS.
†Recommended only for women with IGT or T2DM. Pregnancy category C—use with contraception in women of childbearing age.
‡Reference range varies with laboratory; use lower limit of normal.
BMD, bone mineral density; CVD, cardiovascular disease; ED, erectile dysfunction; PCOS, polycystic ovary syndrome; T2DM, type 2 diabetes mellitus.


**Testosterone Deficiency in Men**

**Disease features**
- Total testosterone <280-300 ng/dL and/or free testosterone <5-9 ng/dL‡
- Signs and symptoms: fatigue, decreased libido, ED, altered mood/cognition, decreased muscle mass and BMD, increased fat mass
- Strongly associated with metabolic syndrome
- Increased risk for T2DM, dyslipidemia, hypertension, and CVD

**Treatment**
- Weight loss
- Testosterone replacement therapy

**Androgen Deficiency and BMI**

**Testosterone and BMI Cohorts**

![Graph showing mean total serum testosterone levels by BMI and metabolic syndrome status](image-url)
Polycystic Ovary Disease

- 1 in 7 couples experience infertility and the majority are associated with obesity
- Ovulatory defects are the explanation in > 50%
- Most patients with obesity and ovulatory defects have PCOS which is most common endocrine dysfunction in premenopausal women
- Prevalence 4-18% depending on diagnostic criteria
- ~50% of patients with PCOS have obesity
- Regardless of whether patients are lean or have obesity, PCOS patients are insulin resistant

PCOS and Female Reproductive and Metabolic Health

**Metabolic**
- Insulin resistance
- Metabolic Syndrome
- Prediabetes
- Type 2 Diabetes
- Dyslipidemia
- Hypertension
- Thrombotic risk
- Coronary Heart Disease
- NAFLD

**Reproductive**
- Dysfunctional uterine bleeding
- Infertility
- Reduced success with reproduction assisted therapy
- GDM risk
- Pre-eclampsia risk
- Higher rate of miscarriage
- Fetal anomalies risk

**Hyperandrogenism**
- Acne
- Hirsutism
- Male-pattern baldness

**Psychological**
- Depression
- Anxiety
- Poor quality of Life

Increasing BMI is associated with worse manifestations of PCOS
Pathophysicsiology of PCOS

**Insulin Resistance**

- Obesity

**Liver**

- Hyperinsulinemia
- Insulin Action Defects
  - IR ser-P

**Pituitary**

- LH/FSH
- Testosterone

**Ovary**

- Testosterone
- Androstenedione

**Adrenal**

- DHEA
- DHEA-S

**Hyperandrogenemia**

**Criteria for Diagnosis of Polycystic Ovary Disease**

<table>
<thead>
<tr>
<th>Diagnostic Components</th>
<th>Clinical Findings</th>
<th>NIH</th>
<th>Rotterdam 2 out of 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydro-androgenism</td>
<td>Clinical hyperandrogenism</td>
<td>Hirsuitism, acne, androgenic alopecia</td>
<td>XX</td>
</tr>
<tr>
<td></td>
<td>Biochemical hyperandrogenism</td>
<td>Decreased total/bioavailable/free testosterone (DHEA -S)</td>
<td>or</td>
</tr>
<tr>
<td>Impaired Ovulation</td>
<td>Oligo-ovulation or Anovulation</td>
<td>Frequent bleeding intervals &lt; 21 days and/or infrequent bleeding intervals &gt;35 days (mid-luteal progesterone)</td>
<td>XX</td>
</tr>
<tr>
<td>Cystic Ovaries</td>
<td>Ovarian size/Morphology</td>
<td>12 or more follicles 2-9 mm and/or increase ovarian volume &gt;10 ml</td>
<td>X</td>
</tr>
</tbody>
</table>

XX = Necessary for diagnosis  X = May be present
Treatment of PCOS

- Anovulation
- Oligo-ovulation
- Infertility
- Dysfunctional Uterine Bleeding
  - Amenorrhea
  - Oligomenorrhea
  - Metrorrhagia
- Acne
- Insulin resistance
- Metabolic Syndrome
- Glucose intolerance
- Acne
- Oligo-ovulation
- Infertility

Clomiphene
Gonadotropins (LH/FSH)
Letrozole
Assisted Reproduction

Combination Oral Contraceptive Pills
Spironolactone (acne)

Metformin

Weight Loss Therapy

Weight Loss with Lifestyle Therapy Improves Metabolism and Hyperandrogenism in PCOS

<table>
<thead>
<tr>
<th></th>
<th>Diet Only</th>
<th>Diet + Aerobic Exercise</th>
<th>Diet + Aerobic + Resistance Exercise</th>
<th>P among groups at end of study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight Loss (%)</td>
<td>-8.6</td>
<td>-10.1</td>
<td>-8.6</td>
<td>NS</td>
</tr>
<tr>
<td>Blood Pressure mmHg</td>
<td>-2.1/-0.1</td>
<td>-5.6/-0.2</td>
<td>-8.7/-0.4</td>
<td>NS</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>-0.56</td>
<td>-0.47</td>
<td>-0.63</td>
<td>NS</td>
</tr>
<tr>
<td>Testosterone (nmol/L)</td>
<td>-0.27</td>
<td>-0.60</td>
<td>-0.35</td>
<td>NS</td>
</tr>
<tr>
<td>SHBG (nmol/L)</td>
<td>+4.2</td>
<td>+6.7</td>
<td>+9.8</td>
<td>NS</td>
</tr>
<tr>
<td>Free Androgen Index</td>
<td>-2.8</td>
<td>-2.6</td>
<td>-2.6</td>
<td>NS</td>
</tr>
</tbody>
</table>

Thompson RL et al. J Clin Endocrinol Metab. 93(9):3373-3380, 2008
**Preconception Interventions in Infertile PCOS: Outcomes following Weight Loss vs OCPs**

RCT: (i) OCPs,  
(ii) Lifestyle intervention for weight loss,  
(iii) OCP + lifestyle  
Followed by standardized ovulation induction with clomiphene and timed intercourse for 4 cycles


**Resumption of Ovulation Associated with a Decrease in Intra-Abdominal Fat in Women with Obesity, PCOS, and Infertility**

Kuchenbecker WKH et al. *Hum Reprod*. 26(9):2505-2512
**Beneficial Effects of Weight Loss to Reverse Infertility**

87 Women with Obesity and Infertility
Completers vs Drop-Outs: Reduced calorie diet and exercise for 6 months

<table>
<thead>
<tr>
<th>Number</th>
<th>67</th>
<th>N= 20 (“drop-outs”)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>37.4</td>
<td>35.9</td>
</tr>
<tr>
<td>Duration infertility</td>
<td>5.4 yr</td>
<td>6.2 yr</td>
</tr>
<tr>
<td>PCOS</td>
<td>79%</td>
<td>72%</td>
</tr>
<tr>
<td>Weight loss</td>
<td>-10.2 kg</td>
<td>-1.2 kg (NS)</td>
</tr>
<tr>
<td>Resume ovulation</td>
<td>80%</td>
<td>0%</td>
</tr>
<tr>
<td>Achieve pregnancy</td>
<td>78%</td>
<td>0%</td>
</tr>
<tr>
<td>Live birth</td>
<td>67%</td>
<td>0%</td>
</tr>
<tr>
<td>Miscarriage rate</td>
<td>18% (75% prior to program)</td>
<td></td>
</tr>
</tbody>
</table>


**Outcomes Following Roux-en-Y Gastric Bypass in Women with Obesity and PCOS**

<table>
<thead>
<tr>
<th>N=24 patients</th>
<th>Before Surgery</th>
<th>2.3 Years After Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>50</td>
<td>30</td>
</tr>
<tr>
<td>HTN</td>
<td>9 patients</td>
<td>2 patients</td>
</tr>
<tr>
<td>T2DM</td>
<td>11 patients</td>
<td>0 patients</td>
</tr>
<tr>
<td>HbA1c</td>
<td>8.2%</td>
<td>5.1%</td>
</tr>
<tr>
<td>GERD</td>
<td>12 patients</td>
<td>0 patients</td>
</tr>
<tr>
<td>Hirsuitism</td>
<td>23 patients</td>
<td>5 patients</td>
</tr>
<tr>
<td>Menstrual Dysfucntion</td>
<td>24 patients</td>
<td>0 patients</td>
</tr>
<tr>
<td>Spontaneous Conception</td>
<td>0/5 patients</td>
<td>5/5 patients</td>
</tr>
</tbody>
</table>

Eid GM et al. Surg Obes Rel Dis. 1(2):77-80, 2005
Retrospective Cohort Study Assessing Weight Loss on Fertility in Patients with Obesity

<table>
<thead>
<tr>
<th>Parameter</th>
<th>LOW Weight Loss Group</th>
<th>HIGH Weight Loss Group</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt; 10%</td>
<td>&gt; 10%</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>34.3</td>
<td>30.7</td>
<td>NS</td>
</tr>
<tr>
<td>PCOS</td>
<td>69%</td>
<td>24%</td>
<td>0.003</td>
</tr>
<tr>
<td>Phentermine</td>
<td>34%</td>
<td>47%</td>
<td>NS</td>
</tr>
<tr>
<td>Metformin</td>
<td>77%</td>
<td>65%</td>
<td>NS</td>
</tr>
</tbody>
</table>

**After Intervention**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>LOW Weight Loss Group</th>
<th>HIGH Weight Loss Group</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conception Rate</td>
<td>54%</td>
<td>88%</td>
<td>0.049</td>
</tr>
<tr>
<td>Spontaneous Conception Rate</td>
<td>17%</td>
<td>35%</td>
<td>0.145</td>
</tr>
<tr>
<td>Time to Conception</td>
<td>231 days</td>
<td>226 days</td>
<td>NS</td>
</tr>
<tr>
<td>Live Birth Rate</td>
<td>37%</td>
<td>71%</td>
<td>0.024</td>
</tr>
</tbody>
</table>


Position of the Practice Committee of the American Society for Reproductive Medicine--2015

“...obese women wishing to conceive should consider a weight management program that focuses on preconception weight loss (to a BMI <35 kg/m²), prevention of excess weight gain in pregnancy, and long-term weight reduction.”

Weight Loss Therapy: PCOS

<table>
<thead>
<tr>
<th>Step 4</th>
<th>Treatment based on clinical judgment</th>
</tr>
</thead>
<tbody>
<tr>
<td>No PCOS</td>
<td>5-10% weight loss</td>
</tr>
<tr>
<td>Metabolic Syndrome Traits</td>
<td>Infertility, Anovulation, Dysmenorrhea</td>
</tr>
<tr>
<td>Health meal pattern, Calorie reduction, Physical activity</td>
<td>Intensive Lifestyle/Behavioral Therapy + Medications</td>
</tr>
<tr>
<td>Overweight/Obesity Stage 0</td>
<td>Obesity Stage 1</td>
</tr>
</tbody>
</table>

Thank You