Overweight and IVF – Strategies to reduce overweight before IVF

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Implications of overweight/obese

- Alterations in hormones

<table>
<thead>
<tr>
<th></th>
<th>Total E2</th>
<th>Free-E2</th>
<th>Progesterone</th>
<th>FSH</th>
<th>LH</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean, %</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overweight</td>
<td>5.30% (4.6)</td>
<td>15.17% (4.1) **</td>
<td>3.35% (3.7)</td>
<td>-15.60% (4.1) **</td>
<td>-10.12% (5.0) *</td>
</tr>
<tr>
<td>Obese</td>
<td>1.39% (6.4)</td>
<td>22.13% (5.6) **</td>
<td>-15.00% (5.1) **</td>
<td>-22.51% (5.7) **</td>
<td>-16.91% (6.9) *</td>
</tr>
<tr>
<td><strong>p-trend</strong></td>
<td>P=0.51</td>
<td>P&lt;0.0001</td>
<td>P=0.04</td>
<td>P&lt;0.0001</td>
<td>P=0.004</td>
</tr>
</tbody>
</table>

Adiposity and sex hormones across the menstrual cycle: the BioCycle Study

Edwina H. Yeung, PhD; Cullin Zhang MD, PhD; Paul S. Albert, PhD; Sunil L. Mumford, PhD; Adjin ’Ye’ PhD; Neil J. Pertkins, PhD; Jean Waclawski-Wendt, PhD; and Eric F. Schlessman, PhD

Research, Eunice Kennedy Shriver National Institute of Child Health and Human Development, Bethesda, Maryland, and Buffalo, New York, USA.

Women were identified using a validated BMI, with overweight defined as BMI (kg/m²) of 25-29.9 and obesity defined as BMI ≥ 30. Sex hormones that were measured included estradiol (E2), free estradiol (Free-E2), progesterone, follicle-stimulating hormone (FSH), and luteinizing hormone (LH). Differences in mean values for each sex hormone were calculated using a general linear model with BMI as the covariate. Differences in area under the curve (AUC) for estradiol and progesterone were calculated using a paired t-test with BMI as a covariate. Significance was set at p<0.05.

Significant differences were observed in both overweight and obese women for all sex hormones measured. Total E2 was significantly higher in overweight compared to obese women (p<0.0001). Free-E2 was also significantly higher in overweight compared to obese women (p<0.0001). Progesterone was significantly lower in overweight compared to obese women (p=0.04). FSH was significantly lower in overweight compared to obese women (p=0.01). LH was also significantly lower in overweight compared to obese women (p=0.004).
Implications of overweight/obese

- Alterations in hormones
- Increased gonadotrophins required per IVF cycle
Implications of overweight/obese

- Alterations in hormones
- Increased gonadotrophins required per IVF cycle
- Decreased numbers of good quality (MII) oocytes, embryos transferred
- Decreased live birth rate
- Increased rates of miscarriage
**Implications of overweight/obese**

<table>
<thead>
<tr>
<th>Variable</th>
<th>&gt;18.50 (0.67–1.96)</th>
<th>18.50–24.99</th>
<th>25.0–29.99</th>
<th>≥30</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ongoing pregnancy</td>
<td>1.15 (0.67–1.96)</td>
<td>1.00</td>
<td>1.06 (0.68–1.66)</td>
<td>1.01 (0.49–2.06)</td>
</tr>
<tr>
<td>Miscarriage rate</td>
<td>1.37 (0.42–4.47)</td>
<td>1.00</td>
<td><strong>2.24 (0.86–5.84)</strong></td>
<td><strong>4.75 (0.70–32.37)</strong></td>
</tr>
<tr>
<td>Live birth</td>
<td>0.54 (0.17–1.79)</td>
<td>1.00</td>
<td><strong>0.51 (0.18–1.41)</strong></td>
<td><strong>0.17 (0.02–1.31)</strong></td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td>37.89 ± 1.87</td>
<td>37.74 ± 3.03</td>
<td>37.59 ± 2.80</td>
<td>37.03 ± 4.41</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>2887 ± 586</td>
<td>3053 ± 613</td>
<td>2932 ± 756</td>
<td>3131 ± 1186</td>
</tr>
</tbody>
</table>
Implications of overweight/obese

- Technical difficulties with egg retrieval
- Concerns for pregnancy
  - Gestational diabetes
  - Pre-eclampsia
  - Pre-term delivery
  - Macrosomia
  - Miscarriage/still birth
- Difficulties monitoring and delivering
Cortisol increases during fasting

<table>
<thead>
<tr>
<th>Study</th>
<th>Hedges’ G (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bergendahl et al.</td>
<td>6.13 [3.79, 8.47]</td>
</tr>
<tr>
<td>Johnstone et al. (Fast)</td>
<td>4.70 [2.51, 6.90]</td>
</tr>
<tr>
<td>Schurgin et al.</td>
<td>3.89 [2.22, 5.55]</td>
</tr>
<tr>
<td>Veldhuis et al.</td>
<td>10.44 [6.69, 14.19]</td>
</tr>
</tbody>
</table>

**Abstract**

Elevated plasma cortisol has been reported following calorie restriction, and may contribute to adverse effects, including stress-induced overeating, but results from published studies are inconsistent. To clarify the effects of cortisol restriction on plasma cortisol, and to assess cortisol as an indicator of stress during calorie restriction, we conducted a systematic review and meta-analysis of published studies in which cortisol was measured following calorie restriction without other manipulations in humans. We further compared effects of fasting, very low calorie diet (VLCD), and other forms of low calorie diet (LCD2), as well as the duration of calorie restriction by meta-regression. Overall, calorie restriction significantly increased serum cortisol concentrations. Meta-regression analysis showed a negative association between serum cortisol level and the duration of calorie restriction, indicating serum cortisol is increased in the initial period of calorie restriction but decreased to the baseline level after several weeks. These results suggest that severe calorie restriction causes activation of the hypothalamus-pituitary-adrenal axis, which may be temporary, but results in elevated cortisol which could mediate effects of stress on brain and metabolic function as well as weight loss.

**Introduction**

Adverse effects of dietary restrictions are a significant public health concern (Garshick & Lerman, 2006). While obesity itself is a health risk, attempts to reduce body weight can increase stress and result in adverse effects, including stress-induced overeating (Pinhook et al., 2010) and cognitive dysfunction (Simonds et al., 2011). Both psychological and physiological, adverse dietary restrictions have been reported (Epel et al., 2003). There have been attempts to assess the increased stress after dietary restrictions by measuring serum cortisol levels. In humans, cortisol can be reliably measured in saliva, blood, and urine and it is cleared by the kidneys (Nico et al., 2011; Stanfield et al., 2012). Elevated cortisol can stimulate appetite, alter mood and memory, and alter peripheral metabolism in favor of weight gain, all of which might be disadvantageous during calorie restriction.

Previous studies suggest that cortisol restriction increases cortisol levels (Delee et al., 1998; Pinhook et al., 2011; Tzourio et al., 2010), but results are inconsistent.

**Methods**

In order to determine eligible studies for the meta-analysis, a MEDLINE search was performed. The following search terms were used: (calorie restriction OR diet restriction) OR (calorie restriction OR diet restriction). Searches in Google scholar and Cincinno Library databases were also conducted to supplement the MEDLINE search. The selected studies were then assessed, and then human studies that did not include cortisol assessment were excluded.
‘caloric restriction overall significantly increased serum cortisol, an effect which is attributable to fasting’
Cortisol affects sex hormones
Cortisol affects sex hormones

‘longer average menstrual cycle length’

‘affected luteinising hormone dynamics’
Cortisol affects sex hormones

‘longer average menstrual cycle length’

‘affected luteinising hormone dynamics’

‘increased feelings of hunger, worse mood, heightened irritability, difficulties concentrating, increased fatigue, eating-related thoughts, fear of loss of control and over eating during non-restricted days’
Cortisol Measurement via Saliva

### Cortisol Levels

<table>
<thead>
<tr>
<th>Sample</th>
<th>Value</th>
<th>Reference Range (nmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample 1 Post Awakening</td>
<td>83.55</td>
<td>7.45-32.56</td>
</tr>
<tr>
<td>Sample 2 (+4 -5 Hours)</td>
<td>23.69</td>
<td>2.76-11.31</td>
</tr>
<tr>
<td>Sample 3 (+4 -5 Hours)</td>
<td>11.91</td>
<td>1.38-7.45</td>
</tr>
<tr>
<td>Sample 4 (Prior to Sleep)</td>
<td>11.77</td>
<td>0.83-3.86</td>
</tr>
<tr>
<td>Sum of Cortisol</td>
<td>130.9</td>
<td></td>
</tr>
</tbody>
</table>

### DHEA Levels

<table>
<thead>
<tr>
<th></th>
<th></th>
<th>Reference Range (nmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DHEA Mean</td>
<td>0.34</td>
<td>0.015-0.150</td>
</tr>
<tr>
<td>DHEA : Cortisol Ratio</td>
<td>0.007</td>
<td>0.015-0.150</td>
</tr>
</tbody>
</table>

### Hormones

<table>
<thead>
<tr>
<th>Hormones</th>
<th>Reference Range (nmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DHEA Sample 1 (am)</td>
<td>0.55 0.25-2.22</td>
</tr>
<tr>
<td>DHEA Sample 3 (pm)</td>
<td>0.12 0.25-2.22</td>
</tr>
</tbody>
</table>
Blood Glucose/ Cortisol

Insulin

Cortisol

Insulin

Cortisol

Blood glucose
Blood Glucose/ Cortisol

- Eating little and often
- Slow-release wholegrain carbohydrates
- Paired with protein and/or healthy fat
- Including healthy snacks
- Restricting carbohydrates in the evening
Mediterranean Diet

• Wholegrains
• Plenty of fresh fruit and vegetables
• Nuts and seeds
• Pulses
• Reduced red meat
• Increased intake of fish
Support

• Focus on what you can have instead of what you can’t
• Practical support
• Ongoing support and feedback
• Encouragement, positive re-enforcement
Recommendations

• Avoid extreme caloric restriction and fasting
• Slow steady weight loss
• Incorporate exercise
• Slow release energy, small meals throughout the day
• Nutrient dense meals to support fertility
  – High in antioxidants, minerals, omega-3
• Support your patients through weight loss