Diet in infertility prevention and management

Jorge E. Chavarro, MD, ScD
Channing Laboratory, Department of Medicine, Brigham and Women’s Hospital and Harvard Medical School. Department of Nutrition, Harvard School of Public Health.
Why Diet?

Clinical motivation
- Few *modifiable* risk factors for infertility known
- Predictors of successful treatment outcomes, including modifiable lifestyle factors.

Public Health Motivation
- Magnitude of the infertility burden
Infertility in the U.S., 2002

- IVF Children: 45,751
- IVF Deliveries: 33,141
- IVF Cycles: 115,392
- Sought help to get pregnant: 1,100,000
- 12 month infertility: 2,100,000
- Impaired fecundity: 7,300,000

Wright et al. MMWR 2005
Chandra et al. Vital Health Stat 2005
Where could nutrition play a role?

- Ovulation disorders 27%
- Semen abnormality 25%
- Tubal defect 22%
- Unexplained 17%
- Endometriosis 5%
- Other 4%

Prevention

Treatment Outcome
Energy balance and infertility

Vigorous physical activity (7h/wk vs. <0.5h/wk):
OR = 0.57 (0.40-0.82)  
Diet and anovulatory infertility

- Insulin sensitivity
  - Macronutrients
- Micronutrient status
  - Iron
  - Folic acid
- Gonadal toxicants
  - Dairy foods (galactose)
  - Caffeine
  - Alcohol
Diet and anovulatory infertility

Increased Risk (RR)

- *Trans* fats (instead of MUFA) (2.31)
- High glycemic load (1.92)
- Low fat dairy (1.85)
- Animal protein (1.39)

Diet and anovulatory infertility

Reduced Risk (RR)

- Folic acid (0.41)
- Non-heme iron (0.60)
- High fat dairy (0.73)
- Vegetable protein (0.78)

Diet alone

Relative Risk (95% CI)

"Fertility Diet" score quintile

Chavarro et al. Obstet Gynecol 2007
Diet, physical activity and BMI

Chavarro et al. Obstet Gynecol 2007
## How much can be prevented

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>%</th>
<th>RR (95% CI)</th>
<th>PAR% (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical activity &gt; 30 min/day</td>
<td>14</td>
<td>0.78 (0.58 – 1.05)</td>
<td>21 (0 – 40)</td>
</tr>
<tr>
<td>BMI 20 – 24.9</td>
<td>54</td>
<td>0.64 (0.53 – 0.78)</td>
<td>21 (12 – 29)</td>
</tr>
<tr>
<td>Diet score Q5</td>
<td>19</td>
<td>0.48 (0.35 – 0.67)</td>
<td>46 (29 – 60)</td>
</tr>
<tr>
<td>4+ factors</td>
<td>14</td>
<td>0.40 (0.27 – 0.59)</td>
<td>55 (36 – 70)</td>
</tr>
<tr>
<td>5+ factors</td>
<td>4</td>
<td>0.31 (0.14 – 0.70)</td>
<td>66 (29 – 86)</td>
</tr>
</tbody>
</table>

*Chavarro et al. Obstet Gynecol 2007*
Nutrition and male fertility

- Alteration of reproductive hormone levels
  - Body weight
- DNA production
  - Folate/methyl donors
- Structural composition of sperm
  - Fatty acids
BMI and reproductive hormones

<table>
<thead>
<tr>
<th></th>
<th>18.5 – 24.9</th>
<th>25 – 29.9</th>
<th>30 – 34.9</th>
<th>≥ 35</th>
<th>P, trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>FSH, IU/L</td>
<td>7.1</td>
<td>7.8</td>
<td>7.9</td>
<td>6.0</td>
<td>0.38</td>
</tr>
<tr>
<td>LH, IU/L</td>
<td>10.4</td>
<td>9.7</td>
<td>9.3</td>
<td>9.4</td>
<td>0.10</td>
</tr>
<tr>
<td>SHBG, nmol/mL</td>
<td>32.7</td>
<td>25.8</td>
<td>21.1</td>
<td>19.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Estradiol, ng/dL</td>
<td>29.5</td>
<td>29.0</td>
<td>33.5</td>
<td>34.5</td>
<td>0.01</td>
</tr>
<tr>
<td>Testosterone, ng/dL</td>
<td>461</td>
<td>401</td>
<td>369</td>
<td>343</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Inhibin B, pg/mL</td>
<td>177</td>
<td>161</td>
<td>147</td>
<td>120</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
## BMI and reproductive potential

<table>
<thead>
<tr>
<th>BMI</th>
<th>Testis Size (mL)</th>
<th>Semen Volume (mL)</th>
<th>Sperm concentration (%)</th>
<th>Sperm count (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 20</td>
<td>-2.0 *</td>
<td>- 0.24 *</td>
<td>-28.1 *</td>
<td>-36.4 *</td>
</tr>
<tr>
<td>20–24.9</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>≥ 25</td>
<td>0.1</td>
<td>-0.003</td>
<td>- 21.6 *</td>
<td>-23.9 *</td>
</tr>
</tbody>
</table>

Jensen et al. Fertil Steril 2004
Weight loss and male fertility

Markers of male fertility potential after bariatric surgery

- Decreased E2, Increased T and free-T (after 2 years)
- Borderline increase in inhibin-B
- Improved sexual quality of life
- No change in LH or FSH

<table>
<thead>
<tr>
<th>Table 1. Clinical history of subjects</th>
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<tr>
<td></td>
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<tr>
<td>Age at bypass operation</td>
</tr>
<tr>
<td>Age at fatherhood</td>
</tr>
<tr>
<td>No. of post-operative spermograms performed</td>
</tr>
<tr>
<td>Age at last post-operative spermogram</td>
</tr>
<tr>
<td>Result of post-operative spermogram</td>
</tr>
<tr>
<td>Result of testicular biopsy</td>
</tr>
</tbody>
</table>

One carbon metabolism emphasizing its relationship with DNA synthesis and methylation
Folate and male fertility

Intake and OAT. Mendiola et al. Fertil Steril 2010
- OR (95% CI) of OAT for increasing tertiles of intake
- 1 (ref), 0.44 (0.09, 2.18), 0.13 (0.02, 0.71). P, trend = 0.02

Seminal plasma levels and DNA fragmentation
Boxmeer et al. Fertil Steril 2009
- \( r = -0.36 \) (among fertile men)

Intake and sperm aneuploidy (21 null, Sex null, XY, XX, YY, 21 di)
Young et al. Hum Reprod 2008
- \( \beta = -3.6\% \) (-6.3\%, -0.8\%) per 100μg in composite aneuploidy
- Mean 52.7 per 10,000 sperm
Folate supplementation

Wong et al. Fertil Steril 2002
Sperm fatty acids and sperm concentration

- Saturated: \( r_S = -0.43 \) (p = 0.01)
- Mono-unsaturated: \( r_S = -0.11 \) (p = 0.52)
- Omega 6 PUFAs: \( r_S = 0.45 \) (p = 0.01)
- Omega 3 PUFAs: \( r_S = 0.75 \) (p < 0.001)
- Trans: \( r_S = -0.44 \) (p = 0.01)

Chavarro et al. ASRM 2009
Diet and treatment outcome

- Body weight
- One carbon Metabolism
- Fatty acids
Odds of Live Birth by BMI

Models adjusted for maternal age, race & ethnicity, number of embryos transferred, and diagnoses

Luke et al. ASRM 2009
One Carbon Metabolism in ART

- Ovarian response
  - $MTHFR$ C677T
  - ↑rFSH dose, ↓E2, oocyte yield
  - ↓E2 (basal and stimulated) in isolated granulosa cells
    - Hecht et al. Fertil Steril 2009

- Embryo development
  - Folicular Fluid Hcy: ↓ day 3 embryo quality
    - Ebisch et al. Hum Reprod 2006
  - Blood B12: ↑ day 3 embryo quality
    - Boxmeer et al. Hum Reprod 2009
One Carbon Metabolism in ART

**Treatment outcome**

- Folate (diet, plasma, RBC), B12 (plasma): Twin birth
- *MTHFR 1298 CC*: ↓ clinical pregnancy, live birth
  - *Haggarty et al. Lancet 2006*
- Folicullar fluid folate: ↑ pregnancy rate
  - *Boxmeer et al. Hum Reprod 2009*
Conclusions

- Diet modification may have a role in:
  - Prevention of certain infertility cases
  - Co-adjuvant to fertility treatment

- Some factors appear to have effects on multiple relevant outcomes
  - Body weight
  - One carbon metabolism
  - Fatty acids

- (Much) More research is needed
Acknowledgements

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- Allison Vitonis
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Jorge E. Chavarro, MD, ScD

Channing Laboratory, Department of Medicine, Brigham and Women’s Hospital and Harvard Medical School. Department of Nutrition, Harvard School of Public Health.