Contraceptive Effectiveness and Obesity

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Program Director for Contraceptive Development
Contraception Research Branch
Disclosures:

NICHD has a Collaborative Research and Development Agreement (CRADA) with HRA Pharma (Paris, France). The goal of the CRADA is to develop Ulipristal Acetate (CDB-2914) for therapeutic indications.

NICHD Principal Investigators: Diana Blithe, PhD & Lynnette Nieman, MD
Types of Obesity – Benign vs At-risk

• Healthy normal weight - BMI 18.5 - 24.9 kg/m²
  0 - 1 metabolic syndrome component:
  1) Triglycerides ≥150 mg/dl
  2) HDL < 50 mg/dl and/or use of lipid-lowering medication
  3) Glucose ≥100 mg/dl
  4) Hypertension and/or use of anti-hypertensive medication

• As of 2012, ~32% of reproductive age women are obese.

• Benign (Metabolically healthy) obesity - BMI ≥30 kg/m²
  0 - 1 metabolic syndrome component (include in contraceptive clinical trials?)

• At Risk (Unhealthy) obesity - BMI ≥30 kg/m²
  ≥2 metabolic syndrome components (exclude from contraceptive clinical trials!)


Midlife for women is age 25-45. Midlife for men?
Risk of Venous Thromboembolism: with Hormonal Contraceptives containing Ethinyl Estradiol (EE), with Obesity or with Pregnancy

<table>
<thead>
<tr>
<th></th>
<th>R.R</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Young women in general</td>
<td>1</td>
<td>1- 5 /10,000/y</td>
</tr>
<tr>
<td>population</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Use of COCs</td>
<td>2.5-5.5*</td>
<td>3-15 /10,000/y</td>
</tr>
<tr>
<td>Low EE dose COC (BMI 20-25)</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Low EE dose COC (BMI 30-35)</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Low EE dose COC (BMI ≥35)</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Pregnancy:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnant Women (BMI ≤25)</td>
<td>12</td>
<td>5-20 /10,000/y</td>
</tr>
<tr>
<td></td>
<td></td>
<td>40-65 /10,000/y</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnant Women (BMI ≥30)</td>
<td>30</td>
<td></td>
</tr>
</tbody>
</table>

May be a higher PE vs DVT rate in obese pregnant women

## Potency of Ethinyl-Estradiol Compared with Estradiol

<table>
<thead>
<tr>
<th>Human assays</th>
<th>Potency relative to E2</th>
<th>E2</th>
<th>EE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum FSH</td>
<td></td>
<td>1</td>
<td>150</td>
</tr>
<tr>
<td>Serum Angiotensinogen</td>
<td></td>
<td>1</td>
<td>330</td>
</tr>
<tr>
<td>Serum SHBG</td>
<td></td>
<td>1</td>
<td>500</td>
</tr>
<tr>
<td>Serum CBG</td>
<td></td>
<td>1</td>
<td>614</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Fish Assays</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><em>in vitro</em> yeast estrogen screen</td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Zebrafish Vitellogenin</td>
<td></td>
<td>1</td>
<td>31</td>
</tr>
<tr>
<td>Zebrafish ovarian somatic index</td>
<td></td>
<td>1</td>
<td>33</td>
</tr>
</tbody>
</table>

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**Lowest Effect Level**

<table>
<thead>
<tr>
<th>Serum FSH</th>
<th>Serum Angiotensinogen</th>
<th>Serum SHBG</th>
<th>Serum CBG</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 ng/L</td>
<td>25 ng/L</td>
<td>50 ng/L</td>
<td>614 ng/L</td>
</tr>
</tbody>
</table>

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**No Effect**

**Fish Assays**

- *in vitro* yeast estrogen screen
- Zebrafish Vitellogenin
- Zebrafish ovarian somatic index

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*b* Caldwell *et al.* Predicted-no-effect concentrations for the steroid estrogens... 2012 *Environ Toxicol Chem* 31:1396-1406.
Conundrum for Providers:

? Provide higher EE dose COCs (30 µg) -
  - THOUGHT to have higher risk of VTE in obese women but
  - MAY be more effective at preventing pregnancy?  

  OR

? Provide lower EE dose COCs (20µg)-
  - MAY be less effective but THOUGHT to have lower risk of VTE?

  OR

? Provide POPs
  - MAY be less effective but HAVE lower risk of VTE?
BMI or Weight?

- Some studies report loss of effect at higher weights rather than BMI.
- BMI is not known for some studies
Contraceptive Patch Studies

Patch studies:

Norelgestromin (150µg)/EE (20µg) - 15 pregnancies in 3319 women

• Failures were clustered in higher weight women
  • 20% of women weighed ≥74 kg (163 lbs) but
  60% (9) of the 15 pregnancies occurred in these women

  ➢ 3% of the study population weighed ≥90 kg (198 lbs)
  – 5 pregnancies

• body weight in a proportional hazards model –  p<0.001

PK Study for IM Injection of Levonorgestrel Butanoate

Edelman et al. unpublished data
Treatment Day of Return to Ovulation

Edelman et al. unpublished data
## Efficacy of LNG rings releasing 20 µg/d

<table>
<thead>
<tr>
<th>Overall pregnancy rate</th>
<th>Pregnancy rate %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women ~40 kg</td>
<td>1.8</td>
</tr>
<tr>
<td>Women ~80 kg</td>
<td>9.8</td>
</tr>
</tbody>
</table>

Levonorgestrel Contraceptive Vaginal Rings

Pregnancy following EC Treatment Stratified by BMI

### Contraceptive Effectiveness and Obesity – FDA meta-analysis

#### 7 Studies of COCs

<table>
<thead>
<tr>
<th>Study</th>
<th>% Obese</th>
<th>Mean BMI</th>
<th>IRR</th>
</tr>
</thead>
<tbody>
<tr>
<td>DES (150)/EE (20,10)</td>
<td>29.9 (NR)</td>
<td>36.9</td>
<td>2.44</td>
</tr>
<tr>
<td>LNG (100)/EE (20,10)</td>
<td>25.7 (NR)</td>
<td>36.1</td>
<td>1.29</td>
</tr>
<tr>
<td>LNG (150) EE (20,25,30)</td>
<td>28.3 (NR)</td>
<td>36.3</td>
<td>1.67</td>
</tr>
<tr>
<td>LNG (150) EE (10)</td>
<td>21.7 (NR)</td>
<td>35.5</td>
<td>1.98</td>
</tr>
<tr>
<td>LNG (90)/EE (20)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NET (800)/EE (25)</td>
<td>14.0 (≤35)</td>
<td>32.4</td>
<td>1.72</td>
</tr>
<tr>
<td>NETA (1000)/EE (10)</td>
<td>16.3 (≤35)</td>
<td>32.3</td>
<td>0.64*</td>
</tr>
<tr>
<td>NGM (180,215,250)/EE(25)</td>
<td>8.5 (≤35)</td>
<td>32.1</td>
<td>0.89*</td>
</tr>
<tr>
<td>NGM (180,250)/EE (25)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NGM (60, 180)/EE (20)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* High Pearl Index in non-obese group

Cochrane Review: Hormonal Contraceptives and Obesity* - Top Tier Methods

• Copper IUD or LNG IUS (not reviewed) - likely not a problem
• Etonogestrel implants - ok within initial 3 year window - (if not challenged by increased metabolism of the progestin)
• LNG implants effective for up to 7 years but first failures were observed in higher weight women.  
  — LNG Implants and Efavirenz
  — Etonogestrel and ARV

• ↑↓ CYP 3A4 enzyme
• ↑ amount of fat tissue where lipophilic steroids can accumulate
• ↑ adipose metabolism

• Injectables ok (IM or SubQ) within the three month window. Additional months?

• COCs – depends on the product...studies disagree
  – both high dose (30 µg EE/150 µg LNG) & low dose (20 µg EE/100 µg LNG)
  --- less effective in FDA meta analysis
  

  – shorter or no pill free interval may improve efficacy, but follicular activity more frequently observed in obese women - more at risk of ovulation if pills are missed.

• Rings
  – LNG rings lost effectiveness in higher weight women
  – Etonogestrel/EE contraceptive vaginal rings – appear to remain above threshold levels for up to 6 weeks


• Patch – significant loss of effectiveness at higher weights

Drug-Drug Interactions - Are Obese Women Closer to the Edge?

- Antibiotics and OCs
- Implants and Efavirenz

Reproductive-age women in 2015?

- Concomitant meds associated with metabolic syndrome components and contraceptives?
- Anti-depressant meds and contraceptives?
- Stimulant meds for ADHD, etc?
- Obesity blood levels and any drug that tips them over the threshold for effectiveness?
Bariatric Surgery

After malabsorptive surgery
  – COCs - Medical Eligibility Criteria = 3
based on predicted lower absorption rate of COCs

Clinical Trials.gov:

PI: Anne Burke - Impact of Gastric Bypass Surgery on the Pharmacokinetics of Oral Contraceptive Hormones. Johns Hopkins Bayview Medical Center Baltimore, Maryland, United States

PI: Anne Bachelot - Pharmacological Evaluation of Hormonal Contraceptive Treatments in Obese Women Before and After Bariatric Surgery. Hôpital Ambroise Paré; Pitié Salpetrière Hospital Paris, France
New to the NIH funding process?

- Getting Started at NICHD
- New Investigators Program
- FOAs: RFAs, PAs, RFPs
- Funding Mechanisms supported by NICHD
  - whom to contact about each
- Forms and Applications
- And more and more ….

https://www.nichd.nih.gov/grants-funding