Disclosures

- Nothing to disclose

- The findings and conclusions in this presentation are those of the author and do not necessarily represent the official position of the US Centers for Disease Control and Prevention.
Objectives

Describe the evidence for women with obesity and:

- safety of combined hormonal contraception
- effectiveness of hormonal contraception
- safety and effectiveness of emergency contraceptive pills
Why are we concerned about hormonal contraceptive use in women with obesity?

- Prevalence of obesity is increasing in the United States
Prevalence\(^1\) of Self-Reported Obesity Among U.S. Adults by State and Territory, BRFSS, 2014

*Sample size <50 or the relative standard error (dividing the standard error by the prevalence) ≥ 30%.

\(^1\) Prevalence estimates reflect BRFSS methodological changes started in 2011. These estimates should not be compared to prevalence estimates before 2011. Obesity: BMI ≥ 30kg/m²
Why are we concerned about hormonal contraceptive use in women with obesity?

- Prevalence of obesity is increasing in the United States

- Women, ages 20-39 years, 2011-2012, US*
  - 32% obesity, all grades (BMI ≥ 30kg/m²)
  - 8% obesity, grade 3 (BMI ≥ 40kg/m²)

*Ogden, 2014
Why are we concerned about hormonal contraceptive use in women with obesity?

- Prevalence of obesity is increasing in the United States
- Women, ages 20-39 years, 2011-2012, US*
  - 32% obese (BMI $\geq 30$ kg/m$^2$)
  - 8% (BMI $\geq 40$ kg/m$^2$)
- Increased risk of pregnancy complications

*Ogden, 2014
Why are we concerned about hormonal contraceptive use in women with obesity?

- Prevalence of obesity is increasing in the United States
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    - 8% (BMI $\geq 40$kg/m$^2$)
- Increased risk of pregnancy complications
- Increased risk of health conditions that may affect safety of contraceptive use
  - CHCs and cardiovascular disease

*Ogden, 2014
Why are we concerned about hormonal contraceptive use in women with obesity?

- Prevalence of obesity is increasing in the United States
  - Women, ages 20-39 years, 2011-2012, US*
    - 32% obese (BMI ≥ 30kg/m²)
    - 8% (BMI ≥ 40kg/m²)
  
- Increased risk of pregnancy complications

- Increased risk of health conditions that may affect safety of contraceptive use

- Obesity may affect drug metabolism

*Ogden, 2014
Outline: Obesity and Hormonal Contraception

- **Obesity and contraceptive safety**
  - CHCs and cardiovascular disease, especially venous thrombosis

- **Obesity and contraceptive effectiveness**
  - Pharmacokinetics
  - Pharmacodynamics
  - Pregnancy rates

- **Emergency contraceptive pills**
  - Safety
  - Effectiveness
OBESITY AND CONTRACEPTIVE SAFETY
Safety: Cardiovascular Disease

- Obesity: increased risk for cardiovascular events
  - Myocardial infarction (MI)
  - Stroke
  - Venous thromboembolism (VTE)

- Combined hormonal contraceptive use: increased risk for cardiovascular events
  - MI
  - Stroke
  - VTE

- Theoretical concern that combined effects of obesity and CHC use could further increase risk beyond individual effects
Safety: MI

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>COC and MI</th>
<th>COC, obesity, MI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tanis, 2001</td>
<td>248 cases 925 controls</td>
<td>Increased risk OR 2.0 (95% CI 1.5-2.8)</td>
<td>BMI $\geq$ vs $&lt;$ 27.3 kg/m$^2$ OR (95% CI)</td>
</tr>
<tr>
<td></td>
<td>Netherlands</td>
<td></td>
<td>High BMI: 3.4 (2.2-5.3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>COC: 2.4 (1.6-2.5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Both: 5.1 (2.7-9.6)</td>
</tr>
<tr>
<td>Sidney, 1998</td>
<td>268 cases 991 controls</td>
<td>No association OR 0.9 (95% CI 0.4-2.2)</td>
<td>No association</td>
</tr>
<tr>
<td></td>
<td>CA and WA</td>
<td></td>
<td>No interaction</td>
</tr>
</tbody>
</table>

- **BMI cut-points for both studies less than obese (27.3 kg/m$^2$).**
- **If there is an increased relative risk, absolute risk likely remains low.**
### Safety: Stroke

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>COC and ischemic stroke</th>
<th>COC, obesity, ischemic stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kemmeren, 2002</td>
<td>203 cases Netherlands 925 controls</td>
<td>Increased risk OR 2.3 (95% CI 1.6-3.3)</td>
<td>BMI $\leq$ 27.3 OR (95% CI)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>High BMI: 1.2 (0.7-2.2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>COC: 2.2 (1.5-3.0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Both: 4.6 (2.4-8.9)</td>
</tr>
<tr>
<td>Sidney, 1998</td>
<td>268 cases CA and WA 991 controls</td>
<td>No association OR 0.7 (95% CI 0.3-1.5)</td>
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</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>No interaction</td>
</tr>
</tbody>
</table>

- BMI cut-points for both studies less than obese (27.3 kg/m²).
- If there is an increased relative risk, absolute risk likely remains low.
Relative Risk of VTE by COC Use and BMI

Ref: BMI ≤25, no-COC
- Highest BMI group, COC
- Lowest BMI group, COC
- Highest BMI group, no-COC

WHO, 1995
Developing countries
Relative Risk of VTE by COC Use and BMI

Ref: BMI ≤25, no-COC
- Highest BMI group, COC
- Lowest BMI group, COC
- Highest BMI group, no-COC

WHO, 1995
Europe
Relative Risk of VTE by COC Use and BMI

Ref: BMI ≤25, no-COC
- Highest BMI group, COC
- Lowest BMI group, COC
- Highest BMI group, no-COC

Adbollahi, 2003
Relative Risk of VTE by COC Use and BMI

Ref: BMI ≤25, no-COC
- Highest BMI group, COC
- Lowest BMI group, COC
- Highest BMI group, no-COC

Pomp, 2007
Relative Risk of VTE by COC Use and BMI

Ref: BMI ≤25, no-COC
- Highest BMI group, COC
- Lowest BMI group, COC
- Highest BMI group, no-COC

Sidney, 2004
(Ref: BMI ≤30, no-COC)
(Ref: BMI >30, no-COC)
Nightingale et al., 2000

- Pooled analysis of UK Mediplus Database and General Practice Research Database
- Includes category for BMI ≥35 kg/m²
- All participants are COC users

<table>
<thead>
<tr>
<th>BMI</th>
<th>Cases</th>
<th>Controls</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;20</td>
<td>34</td>
<td>194</td>
<td>0.8</td>
<td>0.5-1.2</td>
</tr>
<tr>
<td>20-24.9</td>
<td>142</td>
<td>681</td>
<td>1.0 (Ref)</td>
<td>-</td>
</tr>
<tr>
<td>25-29.9</td>
<td>68</td>
<td>216</td>
<td>1.4</td>
<td>1.0-2.0</td>
</tr>
<tr>
<td>30-34.9</td>
<td>32</td>
<td>77</td>
<td>1.8</td>
<td>1.1-2.9</td>
</tr>
<tr>
<td>≥35</td>
<td>21</td>
<td>27</td>
<td>3.1</td>
<td>1.6-5.8</td>
</tr>
</tbody>
</table>
## Estimated Absolute Risk of VTE Among COC Users by BMI

<table>
<thead>
<tr>
<th>BMI</th>
<th>n</th>
<th>OR*</th>
<th>Absolute Risk of VTE (per 100,000 women)</th>
<th>Absolute Risk Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;20</td>
<td>194</td>
<td>0.8</td>
<td>27.0</td>
<td>N/A</td>
</tr>
<tr>
<td>20-24</td>
<td>681</td>
<td>1.0</td>
<td>33.7</td>
<td></td>
</tr>
<tr>
<td>25-29</td>
<td>216</td>
<td>1.4</td>
<td>47.2</td>
<td></td>
</tr>
<tr>
<td>30-34</td>
<td>77</td>
<td>1.8</td>
<td>60.7</td>
<td></td>
</tr>
<tr>
<td>35+</td>
<td>27</td>
<td>3.1</td>
<td>104.5</td>
<td>63-175</td>
</tr>
</tbody>
</table>

- Data from Nightingale to calculate absolute risk of VTE
- By applying odds ratios from other sources, can calculate a range of absolute risk

Trussell et al., 2008; Nightingale et al., 2000
OBESITY AND CONTRACEPTIVE EFFECTIVENESS
Obesity and Contraceptive Effectiveness

- **Pharmacokinetics**
  - Drug levels in the body
  - Ethinyl estradiol, progestin levels

- **Pharmacodynamics**
  - Response to drugs at the site of action
  - Ovarian activity, ovulation, cervical mucus effects

- **Clinical outcomes**
  - Pregnancy
Combined oral contraceptives

- 16 studies that examine pregnancy rates
- 4 presented pregnancy rates by weight or BMI categories
  - None found pattern of increasing pregnancy rate with increasing weight or BMI
- 10 presented relative risks for pregnancy for higher vs lower weight or BMI
Relative risk of pregnancy by higher vs lower weight/BMI among COC users

- Holt 2005
- Holt 2002
- Brunner Huber 2006
- Dinger 2011
- Brunner 2005
- Yamazuki 2015
- Brunner Huber 2007
- Burkman 2009
- Dinger 2009
- Jick 2009

- ≥ 27.3 vs <27.3 BMI
- ≥70.5 vs <70.5 kg
- ≥30 vs < 20 BMI
- ≥ 35 vs <35 BMI
- ≥30 vs < 20 BMI
- ≥ 30 vs <30 BMI
- ≥30 vs < 20 BMI
- ≥ 27.3 vs <27.3 BMI
- Linear BMI
- ≥28 vs < 20 BMI
Combined hormonal patch

- **Yamazaki, 2015**
  - Clinical trial (152 obese women, 1371 non-obese women)
  - Follow-up at least 6 cycles
  - aHR 8.8 (95% CI 2.5-30.5) pregnancy for obese vs non-obese

- **Zieman, 2002**
  - Clinical trial (3319 women)
  - 22,160 treatment cycles; 15 pregnancies
  - Association between baseline body weight and pregnancy (p<.001)
    - 33% of pregnancies among women > 90 kg (< 3% of population)
  - No association between BMI and pregnancy rates
Obesity and Contraceptive Effectiveness

- **COCs**
  - Overall, pregnancy rates not different between obese and normal weight COC users
  - May be subgroups at higher risk – highest BMI or specific formulation
  - If there is an effect, most likely small, may not be clinically significant

- **Patch**
  - Two studies suggest that the patch may be less effective
  - Clinical significance unclear

- **Ring**
  - No pregnancy data

- **Implants, POP, DMPA**
  - No pregnancy data
OBESITY AND EMERGENCY CONTRACEPTIVE PILLS
Morning-after pill may not work for overweight women

By Jacque Wilson, CNN

Updated 9:11 AM ET, Tue November 26, 2013

The morning after pill DOES work as well for overweight women, regulator declares

Clearing Up Confusion: Emergency Contraception and Weight

Dec 16, 2013, 5:38pm  Martha Kempner
ECP Effectiveness and Obesity

- 4 secondary analyses that pooled data from 6 clinical trials, combining various arms
  - UPA and LNG: 2 RCTs (Glasier, 2011)
  - UPA: 2 RCTs (Moreau, 2012)
  - LNG: 2 RCTs (Kapp, 2015)
  - LNG: 3 WHO trials (Gemzell-Danielsson, 2015)
# Results of 2011 analysis

**UPA and LNG**

<table>
<thead>
<tr>
<th>BMI (kg/m²)</th>
<th>Pregnancy Rate % [95% CI]</th>
<th>Odds Ratio [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Overall</td>
<td>UPA</td>
</tr>
<tr>
<td>Normal or underweight (&lt;25)</td>
<td>1.2 [0.8-1.8]</td>
<td>1.1 [0.6-1.9]</td>
</tr>
<tr>
<td>n=2232</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overweight (25-29.9)</td>
<td>1.7 [1.0-3.0]</td>
<td>1.1 [0.4-2.7]</td>
</tr>
<tr>
<td>n=744</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obese (≥ 30)</td>
<td>4.3 [2.8-6.5]</td>
<td>2.6 [1.2-5.6]</td>
</tr>
<tr>
<td>n=469</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Glasier et al. Contraception 2011.*
## Results of 2011 analysis
### UPA and LNG

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</tr>
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<td>n=469</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Odds Ratio [95% CI]

<table>
<thead>
<tr>
<th>BMI (kg/m²)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Obese (≥ 30)</td>
<td>3.6 [1.96-6.53]</td>
<td>2.6 [0.89-7.00]</td>
</tr>
<tr>
<td>Normal or underweight (&lt;25)</td>
<td>Ref</td>
<td>Ref</td>
</tr>
</tbody>
</table>

**Results of 2012 UPA analysis**

<table>
<thead>
<tr>
<th>BMI (kg/m²) Or Weight (kg)</th>
<th>Pregnancy rate % [95% CI]</th>
<th>Adjusted Odds Ratio [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonobese (BMI &lt; 30) n=1830</td>
<td>1.6 [1.1-2.3]</td>
<td>Ref</td>
</tr>
<tr>
<td>Obese (BMI ≥ 30) n=351</td>
<td>3.1 [1.6-5.5]</td>
<td>2.1 [1.0-4.3] p=0.04</td>
</tr>
<tr>
<td>Weight ≤ 85 kg n=1883</td>
<td>1.6 [1.1-2.3]</td>
<td>Ref</td>
</tr>
<tr>
<td>Weight &gt; 85 kg n=298</td>
<td>3.4 [1.6-6.1]</td>
<td>2.2 [1.1-4.6] p=0.03</td>
</tr>
</tbody>
</table>

*Moreau and Trussell. Contraception 2012*
## Results of 2015 analysis (Kapp) LNG data

<table>
<thead>
<tr>
<th>BMI (kg/m²)</th>
<th>Pregnancy rate % [95% CI] following LNG EC</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;20 (n=249)</td>
<td>1.61 [0.44-4.06]</td>
</tr>
<tr>
<td>20-25 (n=873)</td>
<td>1.26 [0.63-2.24]</td>
</tr>
<tr>
<td>25-30 (n=367)</td>
<td>2.45 [1.12-4.60]</td>
</tr>
<tr>
<td>30-35 (n=149)</td>
<td>6.71 [3.26-11.99]</td>
</tr>
<tr>
<td>≥35 (n=93)</td>
<td>4.30 [1.18-10.64]</td>
</tr>
</tbody>
</table>

Kapp et al. Contraception, 2015
Results of 2015 analysis (Gemzell-Danielsson)

LNG data

- 5812 women from 3 WHO trials on LNG ECP
- 56 pregnancies
- No correlation between increasing bodyweight or increasing BMI with pregnancy rate

Table 2: Odds ratios (95% confidence intervals) for pregnancy at selected levels of BMI and bodyweight relative to the odds at the reference point of 22.5 kg/m² and 60 kg. N/A indicates locations of insufficient sample coverage for effect estimation.

<table>
<thead>
<tr>
<th>BMABW</th>
<th>40</th>
<th>45</th>
<th>50</th>
<th>55</th>
<th>60</th>
<th>65</th>
<th>70</th>
<th>75</th>
<th>80</th>
</tr>
</thead>
<tbody>
<tr>
<td>18</td>
<td>2.15 (0.41–11.3)</td>
<td>1.51 (0.63–3.59)</td>
<td>1.83 (0.90–3.74)</td>
<td>2.62 (0.85–8.10)</td>
<td>2.98 (0.39–22.6)</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>20</td>
<td>N/A</td>
<td>1.80 (0.54–5.99)</td>
<td>1.32 (0.73–2.42)</td>
<td>1.26 (0.84–1.89)</td>
<td>1.19 (0.55–2.58)</td>
<td>0.86 (0.11–6.67)</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>22.5</td>
<td>N/A</td>
<td>N/A</td>
<td>2.16 (0.81–5.75)</td>
<td>1.42 (0.88–2.28)</td>
<td>reference point</td>
<td>0.67 (0.35–1.29)</td>
<td>0.38 (0.046–3.16)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>25</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>5.17 (1.03–25.9)</td>
<td>3.10 (1.17–8.17)</td>
<td>1.74 (1.00–3.05)</td>
<td>0.94 (0.55–1.60)</td>
<td>0.50 (0.19–1.31)</td>
<td>N/A</td>
</tr>
<tr>
<td>30</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>13.7 (2.14–87.2)</td>
<td>10.9 (2.06–57.4)</td>
<td>4.53 (0.91–22.6)</td>
<td>1.32 (0.23–7.41)</td>
<td>0.35 (0.030–4.09)</td>
</tr>
<tr>
<td>40</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>12.5 (0.12–1339)</td>
<td>1.02 (0.0022–475)</td>
<td>N/A</td>
</tr>
<tr>
<td>50</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
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<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Gemzell-Danielsson et al. Current Medical Research and Opinion, 2015
“The data are conflicting and too limited to reach a definitive conclusion as to whether effectiveness is reduced in this group [>165 pounds or BMI > 25 kg/m²].”
Safety

- Data on adverse events of ECPs limited; further limited in obese women
- Adverse events did not include complications or comorbidities of obesity, e.g., thrombosis or CVD events
- Little theoretical concern about adverse events, including for women with obesity

Jatlaoui et al., 2016, Contraception.
CONCLUSION
<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No restriction for the use of the contraceptive method for a woman with that condition</td>
</tr>
<tr>
<td>2</td>
<td>Advantages of using the method generally outweigh the theoretical or proven risks</td>
</tr>
<tr>
<td>3</td>
<td>Theoretical or proven risks of the method usually outweigh the advantages – not usually recommended unless more appropriate methods are not available or acceptable</td>
</tr>
<tr>
<td>4</td>
<td>Unacceptable health risk if the contraceptive method is used by a woman with that condition</td>
</tr>
</tbody>
</table>
## US MEC: Obesity

<table>
<thead>
<tr>
<th>Condition</th>
<th>Cu-IUD</th>
<th>LNG-IUD</th>
<th>Implants</th>
<th>DMPA</th>
<th>POPs</th>
<th>CHCs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obesity</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>
# US MEC: Obesity

<table>
<thead>
<tr>
<th>Condition</th>
<th>Cu-IUD</th>
<th>LNG-IUD</th>
<th>Implants</th>
<th>DMPA</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Obesity</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>History of bariatric surgery</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a. Restrictive procedures</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>b. Malabsorptive procedures</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>COC:3</td>
</tr>
</tbody>
</table>

COC: COC, P/R: Progestin-only regimen.
US MEC: Emergency Contraception

- Added “obesity” as a condition in the EC section
- Added ulipristal acetate as a method
- 2016 US MEC available summer 2016

- Copper IUD most effective method of emergency contraception, regardless of weight
- Possible decreased effectiveness of ECPs among women with obesity
- No safety concerns for ECP use among women with obesity
Resources

- CDC evidence-based family planning guidance:
  - http://www.cdc.gov/reproductivehealth/unintendedpregnancy/USMEC.htm
  - http://www.cdc.gov/reproductivehealth/unintendedpregnancy/USSPR.htm

- Sign up to receive alerts!

- Further reading and acknowledgements
  - Jatlaoui TC, Curtis KM. Safety and effectiveness data for emergency contraceptive pills among women with obesity: a systematic review. Contraception 2016 May. [Epub ahead of print]