LESS EFFECTIVE?
Review of hormonal contraception in obese women

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OBJECTIVES
◆ To describe the safety of hormonal contraception among obese women
◆ To review evidence about contraceptive effectiveness among women who are obese

I HAVE NO DISCLOSURES

OBESITY IN THE US
OBESITY

- Defined by body mass index (BMI)
- Calculated using weight and height:

\[
BMI = \frac{\text{weight (kg)}}{[\text{height (m)}]^2}
\]

BMI CATEGORIES

<table>
<thead>
<tr>
<th>Terminology</th>
<th>BMI (kg/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight</td>
<td>&lt; 18.5</td>
</tr>
<tr>
<td>Normal weight</td>
<td>18.5 - 24.9</td>
</tr>
<tr>
<td>Overweight</td>
<td>25.0 - 29.9</td>
</tr>
<tr>
<td>Obese</td>
<td>≥ 30</td>
</tr>
<tr>
<td>Class I</td>
<td>30.0 - 34.9</td>
</tr>
<tr>
<td>Class II</td>
<td>35.0 - 39.9</td>
</tr>
<tr>
<td>Class III</td>
<td>&gt; 40</td>
</tr>
</tbody>
</table>

IMPLICATIONS OF OBESITY

WHAT PERCENTAGE OF YOUR PATIENTS ARE OBESE?

1) 0-10%
2) 11-20%
3) 21-30%
4) 31-40%
5) 41-50%
6) More than 50%
DO YOU THINK THE PERCENTAGE OF OBESE PATIENTS IN YOUR PRACTICE IS INCREASING?

1) Yes
2) No

OBESITY TRENDS* AMONG U.S. ADULTS
BRFSS, 1985

(*BMI ≥ 30, or ~ 30 lbs. overweight for 5' 4” person)

OBESITY TRENDS* AMONG U.S. ADULTS
BRFSS, 1990

(*BMI ≥ 30, or ~ 30 lbs. overweight for 5' 4” person)

OBESITY TRENDS* AMONG U.S. ADULTS
BRFSS, 1995

(*BMI ≥ 30, or ~ 30 lbs. overweight for 5' 4” person)
OBESITY TRENDS* AMONG U.S. ADULTS
BRFSS, 2000

No Data <10% 10%-14% 15%-19% ≥20%

(*BMI ≥30, or ~30 lbs. overweight for 5'-4" person)

OBESITY TRENDS* AMONG U.S. ADULTS
BRFSS, 2005

No Data <10% 10%-14% 15%-19% 20%-24% 25%-29% ≥30%

(*BMI ≥30, or ~30 lbs. overweight for 5'-4" person)

OBESITY TRENDS* AMONG U.S. ADULTS
BRFSS, 2009

No Data <10% 10%-14% 15%-19% 20%-24% 25%-29% ≥30%

(*BMI ≥30, or ~30 lbs. overweight for 5'-4" person)

THE CURRENT STATE OF OBESITY

◆ Two-thirds of Americans are overweight or obese
◆ More than one-third (36.5%) of US adults are obese
◆ In every state, at least 20% of adults are obese
◆ The South has the highest prevalence of obesity
Obese women are at higher risk for pregnancy-related complications including:

- spontaneous abortion
- congenital anomalies
- intrauterine fetal demise
- gestational diabetes
- hypertensive disorders of pregnancy
- venous thromboembolism
- postpartum hemorrhage, and
- cesarean delivery

Risk factors for obesity overlap with risk factors for other health disparities.

**Case Vignette**

JS is a 35yo G0 woman presenting requesting contraception. She is sexually active with 1 male partner. She currently uses condoms inconsistently and does not desire pregnancy at this time. She strongly desires oral contraceptive pills as she has been dissatisfied with other contraceptive methods.
WOULD YOU PRESCRIBE COMBINED ORAL CONTRACEPTIVE PILLS TO JS?

1) Yes
2) No

SAFETY OF COMBINED HORMONAL CONTRACEPTION (CHC) IN OBESE WOMEN

CLINICAL CONSIDERATIONS

Is it effective for me? Is it safe?

SAFETY OF COMBINED HORMONAL CONTRACEPTION (CHC) IN OBESE WOMEN

US MEDICAL ELIGIBILITY CRITERIA (2016): OBESITY

<table>
<thead>
<tr>
<th>Sub-Condition</th>
<th>Cu-IUD</th>
<th>LNG-IUD</th>
<th>Implant</th>
<th>DMPA</th>
<th>POP</th>
<th>CHC</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) BMI ≥ 30</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>b) Menarche to &lt;18 years and BMI ≥ 30</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

Key:
1: no restriction
2: advantages generally outweigh theoretical or proven risks
3: theoretical or proven risks generally outweigh advantages
4: unacceptable health risk
Limited data suggests that obese women who use COCs do not have a higher risk for acute myocardial infarction or stroke than do obese nonusers (Curtis, 2016).

No large, prospective randomized studies comparing the risk of VTE among various doses of estrogen, types of progestin, or routes of administration (ASRM, 2017).

**OBESITY AND VTE**

- Obesity is recognized as a risk factor for VTE in the general population.
- Obese women have a 2-3 fold risk of VTE in comparison to normal weight women.

**Table: Multivariate Hazard Ratio for VTE by BMI (Tsai et al 2002)**

<table>
<thead>
<tr>
<th>BMI</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;25</td>
<td>1.00</td>
</tr>
<tr>
<td>25 to &lt;30</td>
<td>1.47 (1.04-2.10)</td>
</tr>
<tr>
<td>30 to &lt;35</td>
<td>2.23 (1.50-3.11)</td>
</tr>
<tr>
<td>35 to &lt;40</td>
<td>1.52 (0.78-2.96)</td>
</tr>
<tr>
<td>&gt;40</td>
<td>2.71 (1.26-5.84)</td>
</tr>
</tbody>
</table>

**OBESITY, COCs, & VTE**

**Table. Relative risk of VTE by BMI category among combined oral contraceptive users.**

<table>
<thead>
<tr>
<th>BMI</th>
<th>Abdollahi et al.</th>
<th>Nightingale et al.</th>
<th>Lidegaard et al.</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;20</td>
<td>0.5</td>
<td>0.4</td>
<td>0.5</td>
</tr>
<tr>
<td>20–24</td>
<td>0.7</td>
<td>0.6</td>
<td>0.6</td>
</tr>
<tr>
<td>25–29</td>
<td>reference category (1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30–34</td>
<td>1.3</td>
<td>2.2</td>
<td>2.7</td>
</tr>
<tr>
<td>35+</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table. Relative risks and 95% CIs of VTE for combined oral contraceptive users relative to nonusers in each body mass index (BMI) category.**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;25</td>
<td>4.0 (3.2-4.9)</td>
<td>4.6</td>
<td>3.3 (2.0-5.5)</td>
<td>4.3 (2.9-6.2)</td>
</tr>
<tr>
<td>25–29</td>
<td>4.0 (3.2-4.9)</td>
<td>11.3</td>
<td>4.8 (2.6-9.1)</td>
<td>6.0 (3.1-11.3)</td>
</tr>
<tr>
<td>30+</td>
<td>4.0 (3.2-4.9)</td>
<td>6.5</td>
<td>6.0 (3.1-11.3)</td>
<td>8.4 (4.0-17.6)</td>
</tr>
</tbody>
</table>

Trussell, 2008
BEYOND THE PILL

Increased number of cases of VTE among obese women in comparison to non-obese women (Jick et al. 2010)

No data to evaluate risk of VTE among obese women using the combined hormonal ring

INFORMATION GAPS

- No safety data about VTE risk and CHC use in women with BMI > 40 kg/m²
- No data about safety in women with obesity and other co-morbidities

LIKELIHOOD OF VTE

Risk of VTE affected by BMI

THE LARGER PICTURE...

Risks of Pregnancy

Risks of Contraception

Figure 2: Likelihood of Developing a VTE

- Non-Pregnant: Non-CDC user
- CDC user
- Pregnancy:
  - Duration: 8-12 weeks
  - Duration: 12-18 weeks
- Postpartum:
  - Duration: 4-6 weeks
  - Duration: 6-12 weeks

Risk of VTE:

Number of Women with a Blood Clot out of 10,000 Women Years (WY)

* Pregnancy data based on actual durations of pregnancy in the reference studies. Based on a
  model assumption that pregnancy duration is nine months, the use is 7.6/100,000 WY.
CLINICAL CONSIDERATIONS

Will it work for me?

Is it safe?

EFFECT OF OBESITY ON HORMONAL CONTRACEPTION

OBESITY & HORMONAL CONTRACEPTION

Excluded from clinical trials

No evidence that hormonal contraception is ineffective for obese women

Limited studies suggest effectiveness of contraception varies by BMI or body weight

THE INCITING STUDY


FINDING

Women with a body weight of ≥ 70.5 kg had a 60% high risk of oral contraceptive failure than women of lower weight.
CONTRACEPTIVE FAILURE

- Method effectiveness
- Contraceptive failure
- Sexual behavior
- Fecundity
- Contraceptive adherence

BIOLOGICAL PLAUSIBILITY

- Increased metabolic rate
- Increased hepatic clearance
- Increased blood volume
- Increased absorption

Decreased serum drug levels

DIFFERENCES IN PHARMACOKINETICS

- Decreased drug levels
- Ovulation
- Pregnancy

PKs of COCs in obese and normal weight women

FIGURE: Serum concentrations of EE and LNG in 15 normal-weight and 18 obese study participants

Westhoff, 2010

Westhoff, 2012

FIGURE: Serum concentrations of EE2 and ENG in 18 normal-weight and 19 obese contraceptive vaginal ring users

Westhoff, 2009; Westhoff, 2012

• Ovarian suppression similar between obese & non-obese women (Westhoff 2009; Westhoff 2012)
EFFECTIVENESS OF COCS IN OBESE WOMEN

COCHRANE SYSTEMATIC REVIEW

**Aim:** to examine effectiveness of hormonal contraception among women who are overweight and obese

**Methods:** Reviewed studies that reported information on specific contraceptive methods

**Results:** 5 individual studies on COCs, 1 study of pooled data
- 3 showed no difference between BMI and pregnancy risk
- 2 found BMI to be associated with pregnancy risk but in opposite directions
- Pooled analysis: obese women had a 44% high relative risk for pregnancy

**Conclusion:** Most studies did not indicate a higher risk of pregnancy for overweight or obese women

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SYSTEMATIC REVIEW

**Effectiveness of COCs in Obese Women**

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Study Design</th>
<th>Result</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pooled analyses</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yamazaki, 2015</td>
<td>Pooled analysis</td>
<td>aHR 1.44</td>
<td>Fair</td>
</tr>
<tr>
<td>Schramm, 2011</td>
<td>Pooled analysis</td>
<td>No difference</td>
<td>Fair</td>
</tr>
<tr>
<td>Individual studies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vessey, 2001</td>
<td>Prospective cohort</td>
<td>No difference</td>
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<td>Brunner Huber, 2007</td>
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<td>Retrospective cohort</td>
<td>aHR 1.6</td>
<td>Poor</td>
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<tr>
<td>Brunner Huber, 2006</td>
<td>Case cohort</td>
<td>No difference</td>
<td>Poor</td>
</tr>
<tr>
<td>Hult, 2005</td>
<td>Case control</td>
<td>OR 2.17</td>
<td>Fair</td>
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POOLED ANALYSIS: COCS & OBESITY

Table. Effect of obesity (BMI ≥ 30 kg/m²) on pregnancy rate (7 COC trials)

![Pregnancy rates](image-url)
# Systematic Review: Effectiveness of COCs in Obese Women

## Pooled Analyses

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<tr>
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## Individual Studies

<table>
<thead>
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</table>

## Limitations

- Evidence limited to fair to poor quality studies
- Similar methodological limitations
- Self-reported weight & height
- Self-reported pregnancies
- No information on adherence or sexual behavior
- Exclusion of women in the highest BMI categories
- Only 3 studies powered to address association of BMI/weight with pregnancy risk

## Summary: COCs & Obesity

Society of Family Planning (2009): “Obese and overweight users appear to be at a similar or slightly higher risk of pregnancy as compared to normal BMI women.”

- RR 1.5 of contraceptive failure for women with BMI >35
- Estimated failure rate 4.5% (vs. 3%)
- OR 2.17 of contraceptive failure for women with BMI >27
- Estimate 2-4 more pregnancies per 100 woman years in women with BMI >27
EFFECTIVENESS OF COMBINED HORMONAL PATCH

Ethinyl estradiol/ norelgestromin (EE/NGMN) patch

POOLED ANALYSIS: PATCH & OBESITY

Table. Effect of obesity (BMI \(\geq 30\) kg/m\(^2\)) on pregnancy rate (8 COC or patch trials)

<table>
<thead>
<tr>
<th>Weight</th>
<th>COC trials</th>
<th>EE/NGMN patch</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 90kg</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>&gt; 90kg</td>
<td>10</td>
<td>5</td>
</tr>
</tbody>
</table>

CONTRACEPTIVE PATCH:
POOLED ANALYSIS ABOUT EE/NGMN PATCH

Study population by weight
N=3319

- 15 pregnancies: Weight < 90kg
- 10 pregnancies: Weight > 90kg

EFFECTIVENESS OF COMBINED HORMONAL RING

Ethinyl estradiol/etonogestrel (EE/ENg) ring

Zieman 2002
No data comparing effectiveness between obese and non-obese users as large clinical trials excluded obese women.

EFFECTIVENESS OF INJECTABLE CONTRACEPTIVE
Depo-medroxy progesterone acetate (DMPA)

COCHRANE SYSTEMATIC REVIEW DMPA

Jain J et al. Contraceptive efficacy and safety of DMPA-SC. Contraception 2004
- Two large, open-label, Phase 3 studies over 1 year
- Total of 16,023 women-cycles of exposures to DMPA-SC
- Zero pregnancies reported
- Substantial numbers of overweight or obese women.
EFFECTIVENESS OF ETONOGESTREL (ENG) IMPLANT

PHARMACOKINETICS: ENG LEVEL IN OBESE WOMEN

Morrell KM et al (2016)
- Small cross-sectional study of ENG implant
- ENG levels were comparable across BMI groups (normal weight, overweight, and obese)
- No participant fell below threshold for ovulation

EVIDENCE: ENG IMPLANT & OBESITY

Xu H et al (2012), N=1168
- 1 pregnancy in 1377 woman-years of use
- Woman who became pregnant had baseline BMI 30.7
- Substantial inclusion of overweight (28%) and obese women (35%) in study population

Bahamondes L et al (2015), N=1000
- No pregnancies in women ≥ 70 kg
- 3 pregnancies occurred in women < 70 kg
- Small proportion of implant users ≥70 kg was <20% and <8% were obese

BOTTOM LINE: No association between pregnancy risk and weight/BMI among ENG users

EFFECTIVENESS OF LEVONORGESTREL (LNG) IUD
**Evidence: IUD & BMI**

**Xu H et al (2012), N=4200**
- Overall low failure rate (less than 1 pregnancy per 100 woman years)
- Failure rate did not vary by BMI
- Substantial inclusion of overweight (27%) and obese women (35%) in study population

**Gemzell-Danielsson K et al (2015), N=2884**
- LNG-IUS 8 vs. LNG-IUS 13
- BMI not associated with failure rates in either group at 1 or 3 years
- 17% of study population was obese

**Summary:** IUD is highly effective regardless of weight/BMI

**Clinical Considerations**

**Will it work for me?**

**Is it safe?**

**Case Vignette**

JS is a 35yo G0 woman presents requesting contraception. She is sexually active with 1 male partner. She currently uses condoms inconsistently and does not desire pregnancy at this time. She strongly desires oral contraceptive pills as she has been dissatisfied with other contraceptive methods.

**Physical Exam**

- Vital signs:
  - Blood Pressure: 112/72 mmHg
  - Height: 65 inches
  - Weight: 265 lb

- BMI: 44.1 kg/m²

**Would you prescribe combined oral contraceptive pills to JS?**
CASE VIGNETTE

JS is a 35yo G0 woman presents requesting contraception. She is sexually active with 1 male partner. She currently uses condoms inconsistently and does not desire pregnancy at this time. She strongly desires combined hormonal patch as she has been dissatisfied with other contraceptive methods.

PHYSICAL EXAM

Well-appearing woman in no acute distress

Vital signs

Blood Pressure: 112/72 mmHg

Height: 65 inches

Weight: 265 lb

BMI: 44.1 kg/m²

SHARED DECISION-MAKING

Figure. The interdependence of Evidence-Based Medicine and Shared Decision Making and the Need for Both as Part of Optimal Care

CLINICAL CONSIDERATIONS

Will it work for me?

Is it safe?

Is it the best method for me?

SUMMARY

- Limited evidence around contraceptive failure and obesity
- Most evidence finds no association between high BMI/weight and contraceptive failure
- Incorporate discussion about potential risk of decreased effectiveness in obese women in a shared decision model
- Access to contraception should be a priority to women with obesity who do not desire pregnancy