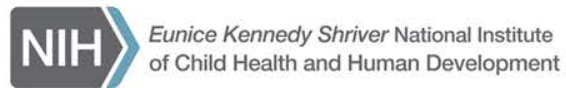


Contraceptive Effectiveness and Obesity

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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.

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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.

Ogden CL *et al.* Prevalence of Childhood and Adult Obesity in the United States, 2011-2012. *JAMA*. 2014;311:806-814

- **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!)

Bleil ME, *et al.* Pubertal Timing, Androgens, and Obesity Phenotypes in Women at Midlife. *J Clin Endocrinol Metab*. 2012 97: E1948-52

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

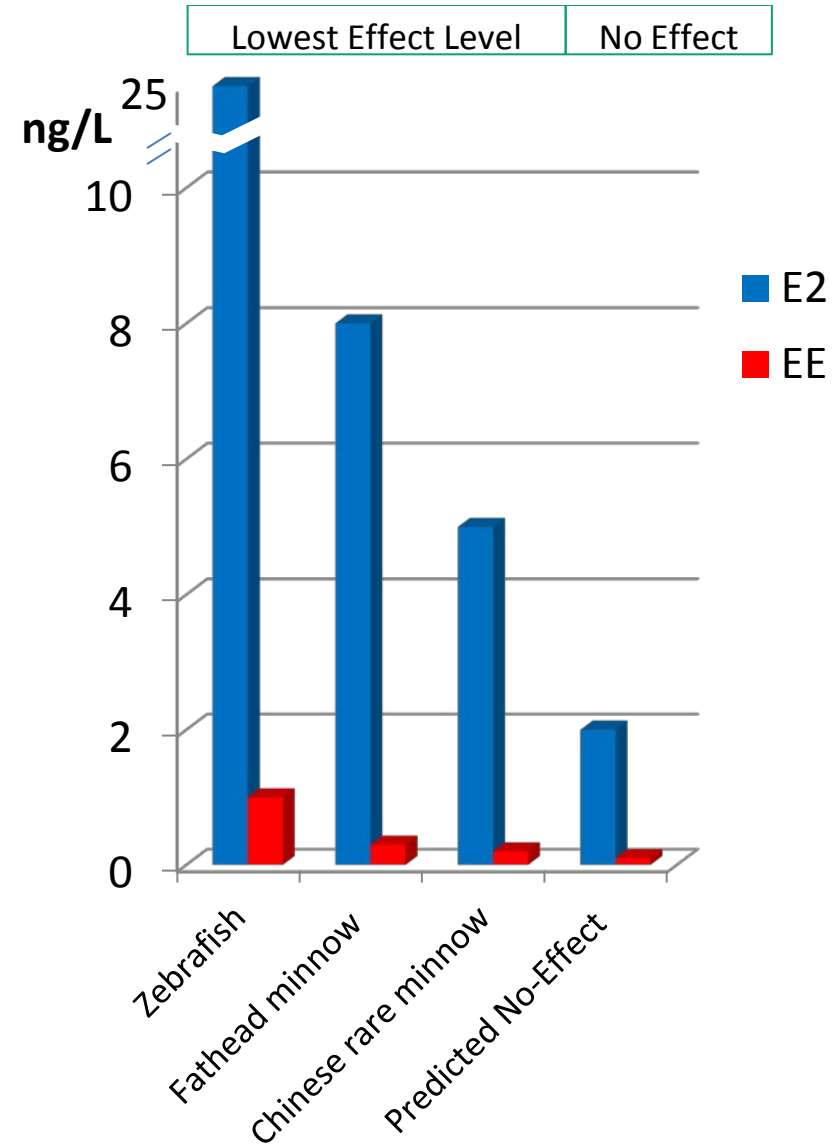
	<u>R.R</u>	<u>Incidence</u>
Young women in general population	1	1- 5 /10,000/y
Use of COCs	2.5-5.5*	3-15 /10,000/y
Low EE dose COC (BMI 20-25)	2	
Low EE dose COC (BMI 30-35)	4	
Low EE dose COC (BMI \geq 35)	8	
Pregnancy:		
Pregnant Women (BMI \leq 25)	12	
During Pregnancy		5-20 /10,000/y
Post Partum		40-65 /10,000/y
Pregnant Women (BMI \geq 30)	30	

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

POTENCY OF ETHINYL-ESTRADIOL COMPARED WITH ESTRADIOL

	Potency relative to E2	
	E2	EE
Human assays ^a		
Serum FSH	1	150
Serum Angiotensinogen	1	330
Serum SHBG	1	500
Serum CBG	1	614

Fish Assays ^b		
<i>in vitro</i> yeast estrogen screen	1	1
Zebrafish Vitellogenin	1	31
Zebrafish ovarian somatic index	1	33



^a Mashchak *et al.* Comparison of pharmacodynamic properties of estrogen formulations. 1982 *Am J Obstet Gynecol* 144:511-18.

^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

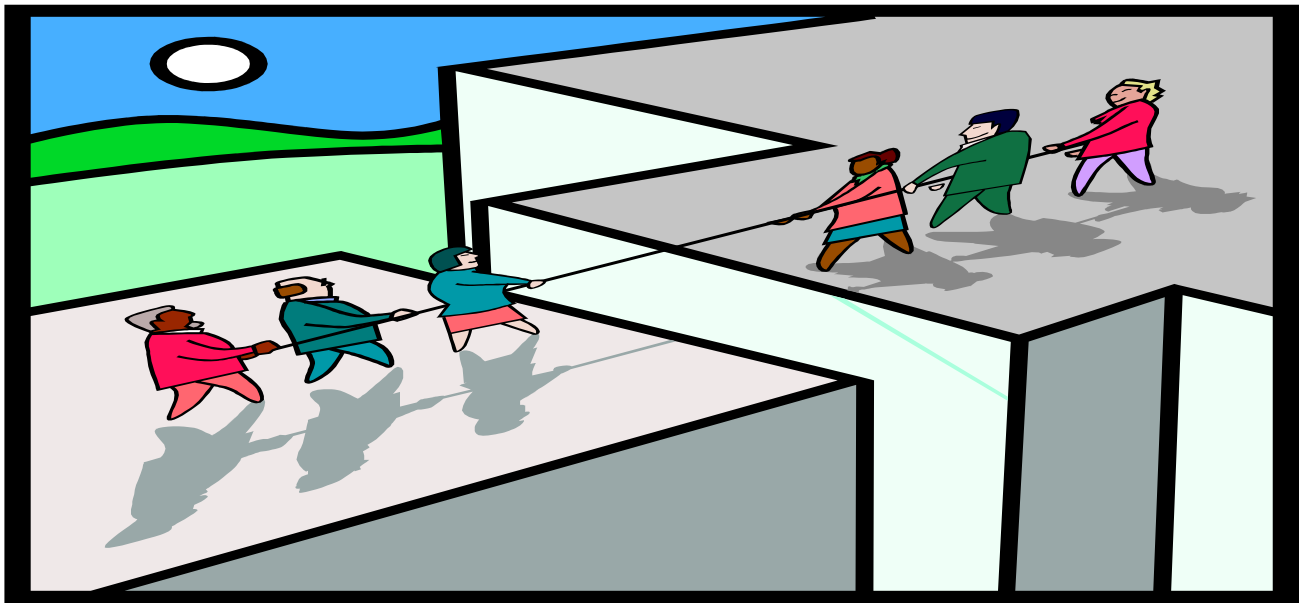
? Provide lower EE dose COCs (20 μg)-

- 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



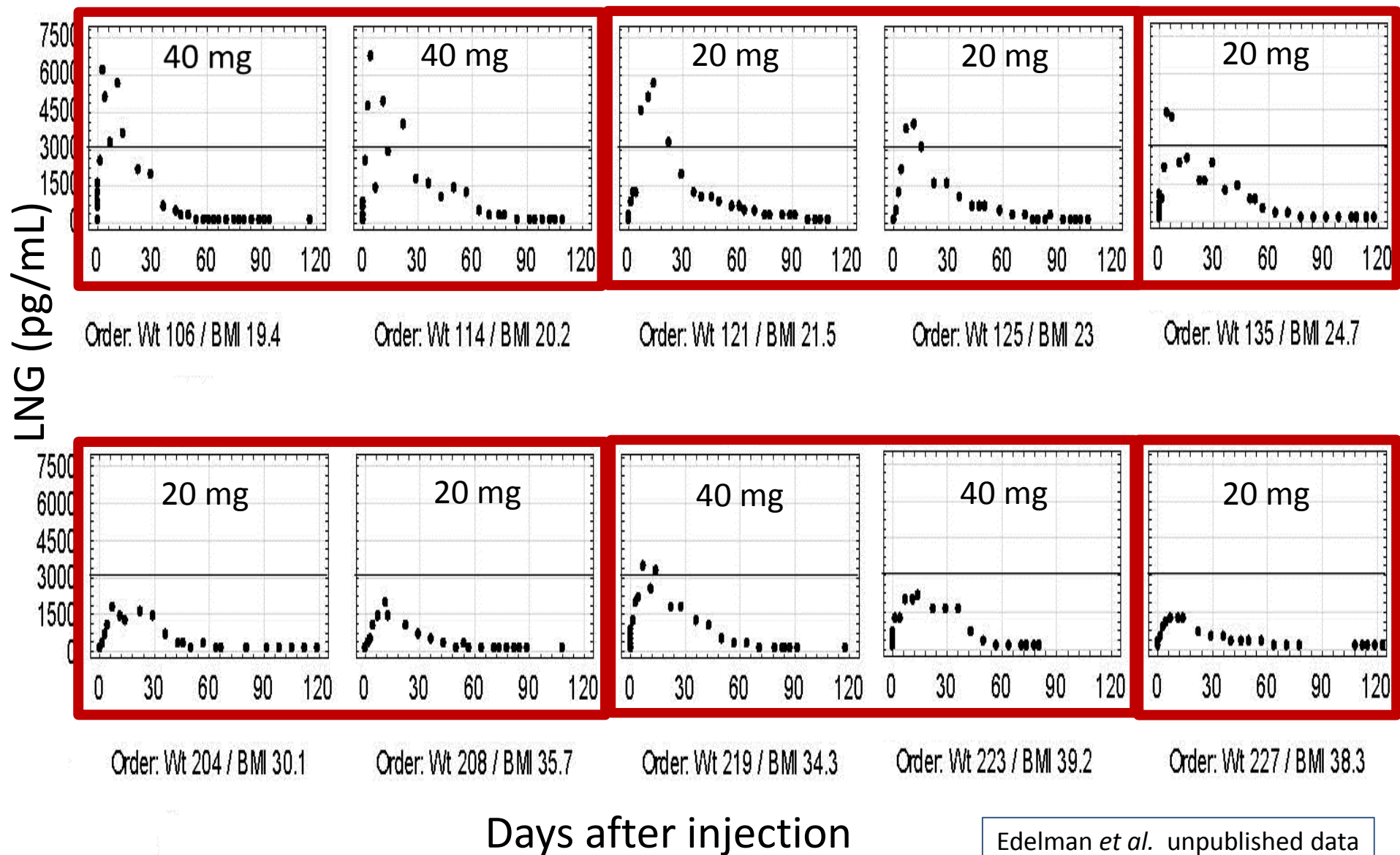
Contraceptive Patch Studies

Patch studies:

Norelgestromin (150 μ g)/EE (20 μ g) - 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





Treatment Day of Return to Ovulation

Ovulation-Free Survival (%)

BMI > 30 —

BMI < 30 ...

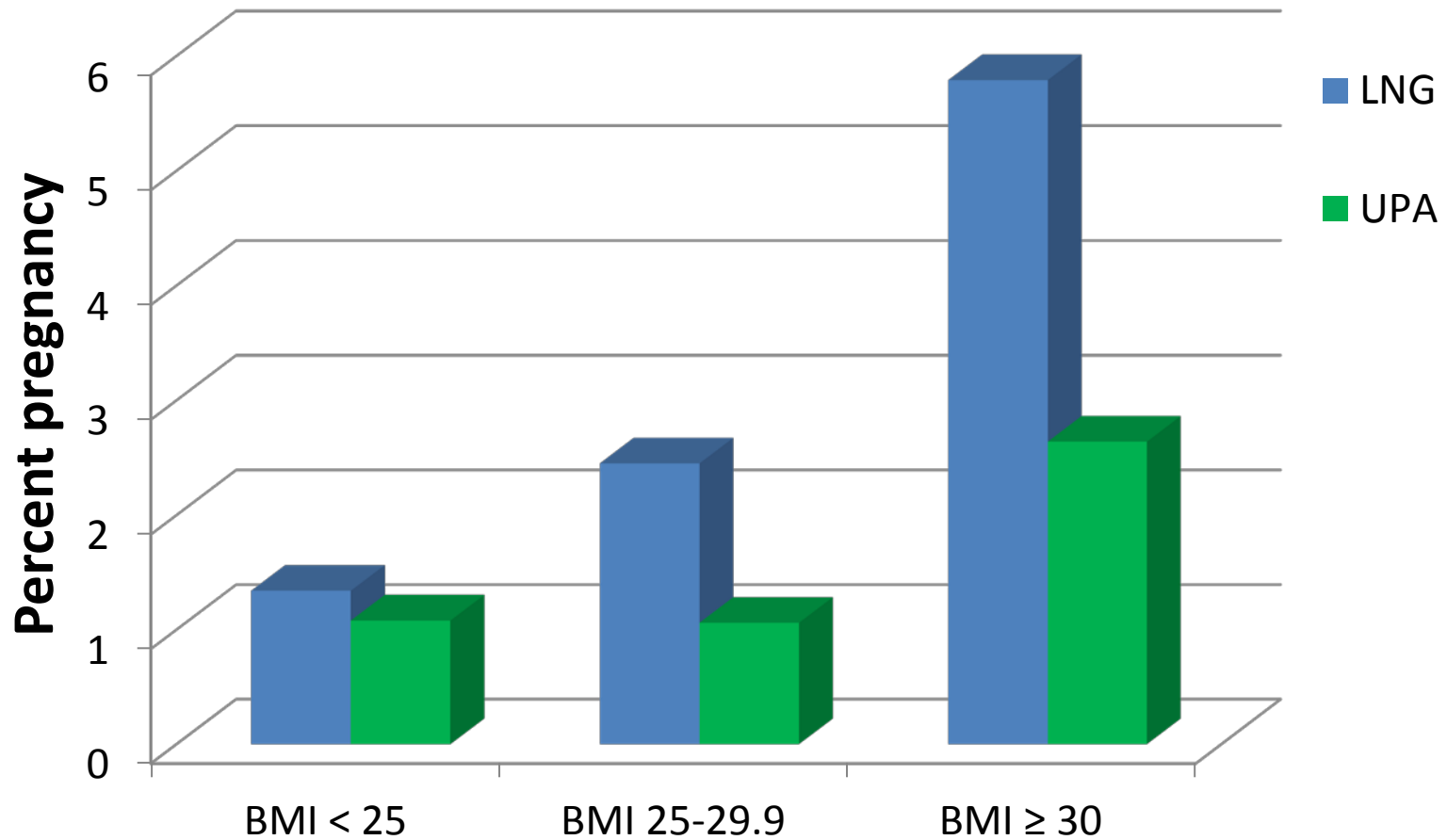


Levonorgestrel Contraceptive Vaginal Rings

Efficacy of LNG rings releasing 20 µg/d

	Pregnancy rate %
Overall pregnancy rate	3.7
Women ~40 kg	1.8
Women ~80 kg	9.8

Pregnancy following EC Treatment Stratified by BMI



Glasier A1, Cameron ST, Blithe D, Scherrer B, Mathe H, Levy D, Gainer E, Ulmann A. Can we identify women at risk of pregnancy despite using emergency contraception? Data from randomized trials of ulipristal acetate and levonorgestrel. *Contraception*. 2011, 84:363-367.

Contraceptive Effectiveness and Obesity – FDA meta-analysis

7 Studies of COCs

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

* 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. Sivin *et al.* *Contraception* 2001 64: 43-49

–LNG Implants and Efavirenz

Scarsi K, *et al.* Efavirenz- but not nevirapine-based antiretroviral therapy decreases exposure to the levonorgestrel released from a sub-dermal contraceptive implant. *J Int AIDS Soc.* 2014 Nov 2;17(4 Suppl)

–Etonogestrel and ARV

Vieira CS, *et al.* Effect of antiretroviral therapy including lopinavir/ritonavir or efavirenz on etonogestrel-releasing implant pharmacokinetics in HIV-positive women. *J Acquir Immune Defic Syndr.* 2014 Aug 1;66(4):378-85

Landolt NK *et al.* Significant decrease of ethinylestradiol with nevirapine, and of etonogestrel with efavirenz in HIV-positive women. *J Acquir Immune Defic Syndr.* 2014 Jun 1;66(2):e50-2.

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

* Lopez LM, Grimes DA, Chen M, Otterness C, Westhoff C, Edelman A, Helmerhorst FM. Hormonal contraceptives for contraception in overweight or obese women. *Cochrane Database of Systematic Reviews* 2013, Issue 4. Art. No.: CD008452.

Cochrane Review – Mid Tier

- 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

Yamazaki M, Dwyer K, Sohban M, Davis D, Kim M-J, Soule L, Willett G, Yu C. Effect of obesity on the effectiveness of hormonal contraceptives: an individual participant data meta-analysis. *Contraception* 2015, Aug 4. pii: S0010-7824(15)00508-9

- 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.

Edelman AB *et al.* Correcting oral contraceptive pharmacokinetic alterations due to obesity: a randomized controlled trial. *Contraception*. 2014 90:550-6.

• 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

Dragoman M, *et al.* Contraceptive vaginal ring effectiveness is maintained during 6 weeks of use: a prospective study of normal BMI and obese women. *Contraception*. 2013 87:432-6

• Patch – significant loss of effectiveness at higher weights

Zieman M, *et al.* Contraceptive efficacy and cycle control with the Ortho Evra™/Evra™ transdermal system: the analysis of pooled data. *Fertil Steril*. 2002 77:S13-18.

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 Salpêtrière Hospital Paris, France



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