Hormonal contraception and obesity

Katharine B. Simmons, M.D., M.P.H.[a] and Alison B. Edelman, M.D., M.P.H.[b]

[a] Department of Obstetrics and Gynecology, University of North Carolina, Chapel Hill, North Carolina; and [b] Department of Obstetrics and Gynecology, Oregon Health & Science University, Portland, Oregon

The rising rate of overweight and obesity is a public health crisis in the United States and increasingly around the globe. Rates of contraceptive use are similar among women of all weights, but because contraceptive development studies historically excluded women over 130% of ideal body weight, patients and providers have a gap in understanding of contraceptive efficacy for obese and overweight women. Because of a range of drug metabolism alterations in obesity, there is biologic plausibility for changes in hormonal contraception effectiveness in obese women. However, these pharmacokinetic changes are not linearly related to body mass index or weight, and it is unknown what degree of obesity begins to affect pharmacokinetic or pharmacodynamics processes. Overall, most studies of higher quality do not demonstrate a difference in oral contraceptive pill effectiveness in obese compared with non-obese women. However, data are scant for women in the highest categories of obesity, and differences by progestin type are incompletely understood. Effectiveness of most non-oral contraceptives does not seem to be compromised in obesity. Exceptions to this include the combined hormonal patch and oral levonorgestrel emergency contraception, which may have lower rates of effectiveness in obese women. The purpose of this review is to summarize evidence on contraceptive use in women with obesity, including differences in steroid hormone metabolism, contraceptive effectiveness, and safety, compared with women of normal weight or body mass index using the same methods. (Fertil Steril® 2016;106:1282–8. ©2016 by American Society for Reproductive Medicine.)

Key Words: Contraception, effectiveness, obesity, pharmacokinetics, safety

Discuss: You can discuss this article with its authors and with other ASRM members at https://www.fertstertdialog.com/users/16110-fertility-and-sterility/posts/11522-hormonal-contraception-and-obesity

T he rising rate of overweight and obesity is a public health crisis in the United States and increasingly around the globe. Obesity now affects 34% of reproductive-age women in the United States and 12% in Western Europe and continues to rise, with nearly 300 million women affected by obesity as of 2008 (1, 2). Obesity is defined by the World Health Organization as a body mass index (BMI) >30 kg/m², whereas overweight is a BMI between 25 and 29.9 kg/m².

People affected by obesity are more likely to experience cardiovascular disease, stroke, type 2 diabetes, osteoarthritis, thromboembolic disease, and cancer, and obesity is the fifth leading cause of mortality worldwide (1). Obese women who become pregnant face an increased risk of gestational hypertension, diabetes, pre-eclampsia, anesthesia complications, and cesarean delivery (33.8% for obese and 47.4% for morbidly obese, compared with 20.7% for normal weight) (3). Fetal complications are also increased, including a higher risk of stillbirth, fetal growth restriction, neural tube defects, and an increase in childhood obesity among the children of obese mothers (3–5). Finally, obese women are less likely to return to prepregnancy weight after a pregnancy, increasing their overall lifetime weight trajectory and adding to their weight-associated problems (5, 6). It is therefore particularly important for women with obesity to have access to safe and effective methods of contraception when they do not desire pregnancy.

The purpose of this review is to summarize evidence on contraceptive use in women with obesity, including differences in steroid hormone metabolism, contraceptive effectiveness, and safety, compared with women of normal weight or BMI using the same methods. Weight and BMI will be used interchangeably throughout this review except where the evidence specifically focuses on one or the other. Weight is a component of BMI, but it remains unclear whether one metric is more important than the other in relation to health outcomes.

CONTRACEPTIVE USE AND OBESITY

Although there has been much anecdotal speculation that the sexual habits and practices of women vary by BMI, this does not seem to be the case. Overweight and obese women have similar rates of contraceptive use as their normal BMI counterparts. The 2002 National Survey of Family Growth demonstrated that the odds of contraceptive nonuse were not significantly different for obese and normal BMI women after adjusting for age, ethnicity, education, and pregnancy desire, with 28.0% of normal BMI women, 25.2% of overweight women, and 25.3%–

http://dx.doi.org/10.1016/j.fertnstert.2016.07.1094

33.0% of obese women reporting use of no method of contraception [7]. A secondary analysis of the 2006 Behavioral Risk Factor Surveillance System family planning module also demonstrated that use of contraception was not associated with BMI after controlling for confounding variables [8]. The contraceptive method mix seems to be similar, with women of different BMI categories choosing contraceptive methods of each effectiveness tier (e.g., most effective including permanent methods, intrauterine devices [IUDs], implants) at similar rates [9].

These studies provide some evidence that contraceptive choice and use is similar among women of varying BMIs, but are these methods equally effective for all women, no matter their size? Contraceptive clinical trials have historically excluded women over 130% of ideal body weight, leaving a gap in understanding of contraceptive efficacy in this population. Additionally, the obesity epidemic increased not just the prevalence of obesity, but the magnitude, making it necessary to study new subcategories of obesity.

FACTORS INFLUENCING CONTRACEPTIVE EFFECTIVENESS

The effectiveness of a contraceptive method is based on adherence to the method, its inherent efficacy, the fecundity of the individual user, and the frequency of coitus. Weight/BMI may affect some or all of these factors, but evidence is still evolving [10].

Adherence

Effectiveness of many contraceptives is dependent on regular action by the user, such as taking a daily pill. Adherence can be particularly challenging with shorter-acting contraceptive methods like the pill, patch, vaginal ring, and injection, as well as with barrier methods. In fact, recent evidence from a large prospective cohort of nearly 10,000 US women receiving no-cost contraception revealed that the typical failure rate for short-acting methods is higher than previously known (4.5% over the first year and nearly 10% by year 3), and approximately 20 times higher than IUDs and implants, which are not user-dependent [11]. It is impossible to determine whether these contraceptive failures were related to adherence or other factors, but the persistent difference between "perfect" failure rates reported in clinical trials and "typical" failure rates like these support a large adherence component in contraceptive failure.

Social factors such as economic status, housing stability, employment, and education may influence a woman's ability to consistently access and utilize contraception such as a daily pill, and nonadherence to contraceptive pills has been associated with residential poverty, obesity, and race/ethnicity [12]. Because obesity is associated with poverty in the United States, it is difficult to conclude whether obesity alone is a risk factor for pill noncompliance.

Drug Metabolism

There are four primary processes involved in the passage of a drug through the body. These include absorption, distribution, metabolism, and excretion. Factors such as sex, age, nutritional status, coadministered drugs, body weight or fat, pregnancy, and disease can alter one or more of these pharmacokinetic (PK) processes. Despite a large increase in obesity rates, the effect of obesity on PK is incompletely understood.

Absorption of drugs may be increased in obesity owing to increased cardiac output leading to increased blood flow to the gastrointestinal tract, as well as faster gastric emptying [13]. This could cause a shorter time to maximum plasma concentration of a drug. Distribution of a drug is altered by changes in lean body mass, adipose tissue, and circulating plasma proteins. Obesity results in a higher volume of distribution for hydrophobic drugs (such as steroids), whereas the volume of distribution for hydrophilic drugs tends to correlate with lean body mass and may be less affected by obesity [13].

Steroid hormones can circulate in unbound or "free" form, or they may bind to plasma proteins. The degree of protein binding contributes to the volume of distribution, with pharmacologic activity of steroid hormones determined primarily by free and albumin-bound forms. Albumin is a major drug-binding protein, and its levels appear unchanged in obese women [13]. However, higher levels of lipoproteins in the obese may compete with drugs for albumin binding sites, potentially leading to higher concentrations of unbound drugs.

Some studies demonstrate an association between obesity and lower levels of circulating sex hormone–binding globulin (SHBG) [14, 15]. Sex hormone–binding globulin is a glycoprotein produced in the liver that binds endogenous estrogens (Es) and androgens, as well as synthetic progestins. Hormone bound to SHBG is not biologically active, so levels of SHBG affect the relative amounts of free and bound Es and progestins that are available to hormonally sensitive tissues [14, 16]. Alterations in SBHG in obesity therefore have the potential to alter distribution of contraceptive steroids [17].

Hepatic metabolism of drugs may be altered in obesity. Metabolism occurs in two phases. Phase 1 includes oxidation, reduction, and hydrolysis, and phase 2 includes conjugation reactions [18]. Alterations in metabolic enzymes have been noted in obese human subjects, specifically a decrease in CYP3A and CYP2E1 activity during phase 1 metabolism. These enzymes are regulated by cytokines, many of which are elevated in the chronic low-grade inflammatory state of obesity. Depending on the drug, phase 1 metabolism may be increased, decreased, or unaffected by obesity. Likewise, increased activity of phase 2 enzymes, such as uridine diphosphate glucuronosyltransferase, may lead to increased total body clearance in obesity [13].

Finally, drug excretion may be altered by obesity. Most drug excretion occurs in the kidney. Renal clearance of drugs increases with BMI, potentially related to higher mean estimated glomerular filtration rates [13]. Biliary excretion of hepatically cleared drugs may also be altered by changes to bile salt secretion and transporters in obesity.

Orally administered hormonal contraceptives. Contraceptive steroid hormones rely on systemic levels to provide contraceptive effect. Orally administered steroids are first subject

to dissolution in the stomach and metabolic transformation by bacterial enzymes in the small intestine. These metabolized and unmetabolized steroids are absorbed from intestinal mucosa into the portal vein blood supply and are then delivered to the liver. Once in the liver, metabolizing enzymes transform both unmetabolized and metabolized steroids (first-pass metabolism). After this first pass through the liver, some of the original steroid hormone remains unmetabolized and is released into the systemic circulation along with steroid metabolites. Bioavailability is the proportion of the originally ingested steroid hormone that reaches the systemic circulation after first-pass metabolism. Bioavailability for ethinyl estradiol (EE), the E component of most combined hormonal contraceptives (CHCs), ranges from 25% to 65%, and for most synthetic progestins is between 70% and 90% (18).

In normal weight women, 90% of oral EE is absorbed from the stomach and small intestine during the first hour after ingestion. Peak blood levels are achieved in many women by 1–2 hours, though in some women it can take up to 6 hours to reach maximum circulating levels (18). As it undergoes first-pass hepatic metabolism, some EE molecules undergo 2-hydroxylation, mediated by cytochromes P450 CYP3A4 and CYP2C9. Ethinyl estradiol and its hydroxlyated metabolites are then conjugated to sulfates, which circulate systemically and undergo enterohepatic recirculation, and glucuronides, which are renally excreted. Both unmetabolized EE and EE sulfates circulate and undergo additional hepatic passes, where the steps are repeated. Elimination half-life for EE ranges from 6 to 27 hours for normal weight women. Of note, there is significant variation in systemic EE exposure both within and between individuals because of differences in CYP enzyme activity, and ethnic differences in metabolite composition have also been observed (19).

There are many synthetic progestins used in hormonal contraception (HC), and these differ in their metabolism and pharmacokinetics. Some progestins are "prodrugs," meaning they become systemically active only after metabolism to an active form. Oral progestins are well absorbed and undergo hepatic first-pass metabolism like EE. Time to maximum concentration in systemic circulation is 1–3 hours (20). Norethindrone has a half-life of 8–12 hours, whereas most others have half-lives between 12 and 24 hours (19).

Contraceptive steroid hormones alter production of several hepatic proteins, including SHBG, as they pass through the liver. Estrogens are the most potent inducing factors for SHBG. Increases in SHBG levels have been reported in all formulations of CHCs (21, 22). By contrast, progestins have a varying effect on SHBG, usually decreasing SHBG levels. Importantly, levonorgestrel (LNG) alone reduces serum SHBG levels, and when coadministered with E it diminishes the estrogenic increase of SHBG (16). The total change in SHBG observed with HC is determined by the sum of the E and progestin effects. The contraceptive effect of HCs relies on sufficient free progestin to provide ovarian suppression even in the face of rising SHBG.

The interaction of oral contraceptives, SHBG, and obesity with oral contraceptive PK is complex and incompletely understood. Changes to PK parameters in obese women taking a 20-μg EE/100-μg LNG pill include a longer half-life, and

longer time to reach study state than normal weight controls (23). An increase in half-life translates to a longer time to steady state, which may alter the time to reach levels sufficient for ovulatory suppression, providing a possible mechanism for contraceptive failure. In a recent cohort of obese women, mean time to reach LNG steady state was 13.6 days (SD 8.4), compared with a mean of 5.3 days for normal weight controls (SD 1.9) (23). Given that ovulation generally occurs around cycle day 14, this could indicate that serum levels of LNG may not reach a threshold to successfully prevent ovulation in obese users initiating combined oral contraceptives (COCs), or after the 7-day hormone-free interval in typical cyclic COCs.

Non-oral hormonal contraceptives. Contraceptive steroids including EE and synthetic progestins delivered via parenteral routes (transdermal, vaginal, IM, subcuticular, subdermal, or intrauterine) achieve steady state rapidly and maintain relatively constant plasma concentrations (24). For non-oral methods, steady state plasma concentrations of steroid hormones are the relevant PK parameter. As in oral formulations, obesity can affect steady state levels through differences in plasma protein binding and elimination rates.

Several routes of progestin administration do not seem to result in lower total contraceptive steroid levels in obese compared with normal weight women. Although one study of 13 women demonstrated that plasma etonogestrel (ENG) concentrations in users of the ENG subdermal implant were nearly 48% lower in obese women (median BMI 41 kg/m^2) than normal weight women, multiple larger studies did not demonstrate a difference in ENG levels across BMIs after 1 year of use or during extended use into years 4 or 5 (25–27). Etonogestrel administered via combined hormonal vaginal ring also resulted in serum levels that were no different in obese vs. normal weight women over a single cycle (28). Similarly, IM and SC medroxyprogesterone acetate levels do not seem to differ by BMI (29–31). However, all of these studies measured total hormonal levels (not free levels), so these findings may not be directly applicable to clinical or pharmacodynamics outcomes and may not be translatable to other progestins with different protein binding patterns (17).

By contrast, PK of some other non-oral progestins does vary by BMI. Norelgestromin administered via transdermal patch resulted in lower progestin levels as body weight increased in a single study, although no other details were provided (32). Likewise, one study demonstrated a trend toward lower LNG plasma levels in obese women as BMI increased in users of the LNG IUD, although this is unrelated to the IUD's contraceptive mechanism (33).

Given the range of PK alterations in obesity, there is certainly biologic plausibility for PK-based changes in HC effectiveness in obese women.

EFFECTIVENESS OF HCs

In combined hormonal methods, contraceptive effect is provided by both a synthetic progestin and an E. The progestin component provides ovulation suppression through suppression of LH at the pituitary. Additional ovulation suppression

is provided by the EE component, which suppresses FSH release to prevent formation of a dominant follicle. Most progestin-only methods rely on progestin suppression of LH or changes to cervical mucus for contraceptive effect. Given the myriad changes in steroid hormone PK in obesity, there is concern whether obese women using HC may face a higher risk of contraceptive failure than normal weight women. However, evidence on effectiveness of HC in obese women is primarily reassuring, with most studies showing effectiveness similar to that of normal weight women for most formulations (34).

Oral Contraceptive Pills

Studies of effectiveness of oral contraceptive pills (OCPs) in obese women are conflicting (34). The term COC refers specifically to combined oral contraceptive pills, whereas the term OCP refers to all oral contraceptives, including progestin-only pills. Most studies demonstrating an association between increasing BMI and OCP failure had significant limitations, including failing to differentiate between PK factors and behavioral factors, such as pill compliance, and use of self-reported weight remote from the time of contraceptive failure (35–37). Multiple population-level and observation studies that better controlled for exposure classification (weight, adherence) and outcome ascertainment (pregnancy) did not show a difference in effectiveness between normal weight and obese women, though many of these did not include women in the highest categories of obesity (>BMI 35 kg/m^2) (38–41).

A recent meta-analysis of phase 3 trials submitted to the US Food and Drug Administration (FDA) combined efficacy data for seven COC formulations and reported a 44% higher relative risk of pregnancy in obese women compared with non-obese women (adjusted hazard ratio [aHR] 1.44, 95% confidence interval [CI] 1.06–1.95) (42). However, the Pearl indices for obese and normal weight women were similar (3.14 obese vs. 2.53 non-obese), suggesting this finding may have limited clinical significance.

On the basis of PK differences in progestin metabolism in obese women, it is possible that effectiveness of OCPs in obese women varies by progestin. Several large, prospective studies demonstrating no difference in effectiveness combined multiple progestin formulations, which may have obscured differences by pill type (43, 44). Others that did show a difference by obesity status (42, 45) may have biased their effect size toward the null by combining multiple formulations. Because of its high level of binding to SHBG, oral LNG may be the progestin most at risk of reduced effectiveness in obesity, but no studies specifically addressed effectiveness of this progestin in obese vs. non-obese women in a cyclic COC.

Finally, dosing strategy may also play a role in contraceptive effectiveness in obese women, given observed PK differences in time to steady state in obesity (23). In a PK and pharmacodynamics study, eliminating the hormone-free interval for obese women using a 20-μg EE/100-mg LNG pill resulted in normalization of PK parameters and equivalent ovarian suppression as in normal weight women taking the same pill in a cyclic fashion. No population-level studies have addressed dosing strategies as a predictor of contraceptive failure. However, a large prospective, cohort study of multiple pill formulations dosed in a 21/7-day fashion reported a higher failure rate in obese vs. non-obese women (aHR 1.5, 95% CI 1.3–1.8), whereas drosperinone-containing pills dosed in 24/4-day fashion showed no difference by obesity status (45).

Overall, most studies of higher quality do not demonstrate a difference in OCP effectiveness in obese compared with non-obese women. However, data are scant for women in the highest categories of obesity, and differences by progestin type are incompletely understood. It is plausible that the large impact of adherence issues with short-term methods like pills mask the smaller impact that obesity may have on effectiveness.

Non-oral Combined HCs

Limited evidence supports an increased risk of contraceptive failure in obese women using the transdermal contraceptive patch containing EE/norelgestromin. A pooled analysis of early multicenter, open-label studies reported 15 pregnancies in 3,319 women over 6–13 cycles of follow-up (32). These contraceptive failures occurred disproportionately in obese women; five pregnancies occurred in women over 90 kg, who represented less than 3% of the study population. Likewise, in an analysis of data submitted to the FDA for 1,523 women using this patch, obese women (n = 152) had a higher risk of pregnancy than non-obese women after adjusting for age and race (aHR 8.80, 95% CI 2.54–30.5) (42). However, absolute pregnancy rates were still low in both studies across all weight groups, and the EE/norelgestromin patch provides superior contraception to barrier methods even in obese women.

The only study to report contraceptive failure of the EE/ENG vaginal ring in obese vs. non-obese women was a secondary analysis of phase 3 efficacy trials. The pregnancy rate for women in the highest decile of weight (>167 lb) was 1.2%, with no pregnancies reported in the heaviest women (189–272 lb) (46). On the basis of this limited evidence, the EE/ENG ring seems to have similar efficacy in obese and non-obese women.

Subdermal Contraceptive Implants

Pregnancy rates in users of the single rod ENG implant are similar in overweight and obese compared with normal weight women over 4 years of implant use. In a secondary analysis of 1,168 implant users in the Contraceptive CHOICE project, 28% were overweight and 35% obese (47). One pregnancy occurred in a woman with a baseline BMI of 30.7 kg/m^2 4 days after implant placement; this likely represented an unrecognized luteal phase pregnancy. Cumulative failure rates over 3 years were 0.00 per 100 woman years for normal and overweight women, and 0.23 per 100 woman years for obese women. In a follow-up study of prolonged implant use (up to 5 years), 237 women continued use of the ENG implant for a total of 229.4 women years of use beyond the

3-year FDA approval, of whom 25% were overweight and 46% were obese (27). No pregnancies occurred during the period of prolonged use, leading to an estimated failure rate of 0 (97.5% one-sided CI 0, 1.61) over all BMIs. Overall these data are reassuring that contraceptive failure is extremely rare with the ENG implant in obese as well as normal weight women over 4 years of continuous use.

Progestin Injectables

Limited data suggest that pregnancy rates do not change by body weight in depo-medroxyprogesterone acetate (DMPA) users. One multicenter trial of DMPA in 846 women (over 389.5 woman-years) reported a pregnancy rate of 0.7/100 woman-years across all women, and baseline body weight was not related to contraceptive failure (48). However, less than 5% of this population was over 80 kg, so this may not be generalizable to women of higher body weights. No studies have specifically compared IM DMPA failure rates in obese vs. normal weight women (34).

The phase 3, open-label studies of DMPA SC included 1,065 women over 1 year. Trials in the Americas included 18% of users with a BMI >30 kg/m^2 (range, 30–57 kg/m^2), whereas trials in Europe/Asia included 6% obese women (31). No pregnancies were observed in either trial location, suggesting high contraceptive effect regardless of body weight.

Oral Emergency Contraception

A 2016 systematic review addressed effectiveness of oral emergency contraception (EC) in obese compared with normal weight women (49). Authors identified four pooled secondary analyses of poor to fair quality, three studying LNG and two ulipristal acetate. Women with obesity were at higher risk of pregnancy after using LNG than normal weight women in two of three studies, whereas obese women did not have a statistically significant increased risk of pregnancy after ulipristal acetate.

In a PK analysis, Edelman et al. (50) reported that whereas a single dose of LNG EC in obese women resulted in a significantly lower LNG maximum serum concentration than in normal weight women (50% lower), doubling the dose of LNG EC from 1.5 to 3 mg in obese women (median BMI 39.5 kg/m^2) normalized the PK parameters to that of the normal weight women. Although they did not study any pharmacodynamics or clinical endpoints, this is early evidence that a higher dose of LNG may improve the efficacy of LNG EC in obese women.

Women with obesity desiring EC should be counseled on the effectiveness of all methods, including the copper IUD, which remains the most effective option for EC regardless of body weight (51).

Progestin Intrauterine Devices

Because IUDs act primarily via local mechanisms and do not rely on systemic drug levels, their effectiveness should not vary by weight/BMI. This expectation was confirmed in a large prospective, cohort study in which effectiveness of IUDs was very high and did not vary by BMI (47). Placement of IUDs in obese women may be more difficult owing to poor visualization of the cervix, but optimization of visualization with speculum and instrument choice and vaginal wall retraction can usually lead to successful placement (52).

SAFETY

Both the World Health Organization and the US Medical Eligibility Criteria for Contraceptive Use consider CHCs category 2 for obesity (advantages generally outweigh theoretical or proven risks) and progestin-only methods as category 1 (unrestricted use) (with the exception of DMPA in adolescents, which is category 2) (53, 54). The primary safety concerns for obese women utilizing HC are cardiovascular risks from exogenous E, including acute myocardial infarction (AMI), stroke, and venous thromboembolism (VTE).

There is conflicting evidence from two studies whether the risk of AMI is increased in obese users of CHCs compared with non-obese users or obese nonusers (55), but overall absolute risk of AMI is low in women of reproductive age regardless of BMI (56). The risk of stroke among CHCs users does not seem to vary by BMI, though evidence is limited to one published study (57).

Obesity and CHC use are both risk factors for VTE. At baseline the risk of VTE increases as the degree of obesity increases (55). Use of CHCs (among non-obese women) increases the risk of VTE by approximately three times, from approximately 4.5 to 14.5 per 10,000 woman-years (58, 59). Whether obesity further modifies the VTE risk in CHC users is less clear. In a recent systematic review of cardiovascular events in obese users of COCs, obese women using COCs had 5 to 8 times the risk of VTE compared with obese nonusers, and 10 times the risk compared with normal weight nonusers (55). It is difficult to estimate the absolute risk of VTE among obese women using COCs owing to heterogeneity of risk estimates for these conditions; however, it is likely higher than that reported for normal BMI COC users. All women using CHCs, no matter their weight, should be counseled on the risk of VTE. Obese women utilizing these methods face a relative higher risk than their normal weight counterparts and should be counseled accordingly. However, pregnancy and the postpartum state are also risk factors for VTE across all BMI categories, increasing the risk by 5-fold and 60-fold, respectively, compared with nonpregnant women, which should also be addressed with women during counseling on contraceptive risks (60).

CONCLUSION

To conclude, all women, no matter their weight or BMI, who are at risk of unintended pregnancy can and should be offered the full range of contraceptive methods available. Long-acting reversible methods, such as IUDs and progestin implants, offer the lowest failure rate with minimal risk, and seem to offer equivalent effectiveness across BMI and weight categories. Despite changes to the metabolism of contraceptive steroid hormones in obesity, effectiveness of most contraceptive methods does not seem to be compromised.

Exceptions to this include the combined hormonal patch and LNG-based oral EC, which may have lower rates of effectiveness in obese women (though still superior to barrier methods or no contraception).

REFERENCES

1. World Health Organization. Obesity and overweight. Available at: www.who.int/mediacentre/factsheets/fs311/en/index.html. Accessed June 20, 2016.

2. Ogden C, Carroll M, Kit B, Flegal K. Prevalence of obesity in the United States, 2009-2010. NCHS Data Brief 2012;82:1–8.

3. Weiss JL, Malone FD, Emig D, Ball RH, Nyberg DA, Comstock CH, et al. Obesity, obstetric complications and cesarean delivery rate—a population-based screening study. Am J Obstet Gynecol 2004;190:1091–7.

4. Olson G. Obesity and implications for future generations. Am J Obstet Gynecol 2012;206:255–7.

5. Phelan S. Pregnancy: a "teachable moment" for weight control and obesity prevention. Am J Obstet Gynecol 2010;202:135.e1–8.

6. Kominiarek M. Bariatric surgery and pregnancy. ACOG Practice Bull 2009:1–9.

7. Vahratian A, Barber JS, Lawrence JM, Kim C. Family-planning practices among women with diabetes and overweight and obese women in the 2002 National Survey for Family Growth. Diabetes Care 2009;32:1026–31.

8. Schraudenbach A, McFall S. Contraceptive use and contraception type in women by body mass index category. Womens Health Issues 2009;19: 381–9.

9. Kaneshiro B. Contraceptive use and sexual behavior in obese women. Semin Reprod Med 2012;30:459–64.

10. Simmons KB, Edelman AB. Contraception and sexual health in obese women. Best Pract Res Clin Obstet Gynaecol 2015;29:466–78.

11. Winner B, Peipert JF, Zhao Q, Buckel CM, Madden TE, Allsworth JE, et al. Effectiveness of long-acting reversible contraception. N Engl J Med 2012; 366:1998–2007.

12. Westhoff CL, Torgal AT, Mayeda ER, Shimoni N, Stanczyk FZ, Pike MC. Predictors of noncompliance in an oral contraceptive clinical trial. Contraception 2012;85:465–9.

13. Cho SJ, Yoon IS, Kim DD. Obesity-related physiological changes and their pharmacokinetic consequences. J Pharm Invest 2013;43:161–9.

14. Stanczyk FZ, Grimes DA. Sex hormone-binding globulin: not a surrogate marker for venous thromboembolism in women using oral contraceptives. Contraception 2008;78:201–3.

15. Hautanen A. Synthesis and regulation of sex hormone-binding globulin in obesity. Int J Obes Relat Metab Disord 2000;24(Suppl 2):S64–70.

16. Hammond GL, Abrams LS, Creasy GW, Natarajan J, Allen JG, Siiteri PK. Serum distribution of the major metabolites of norgestimate in relation to its pharmacological properties. Contraception 2003;67:93–9.

17. Cherala G, Edelman A, Dorflinger L, Stanczyk FZ. The elusive minimum threshold concentration of levonorgestrel for contraceptive efficacy. Contraception 2016;94:104–8.

18. Edelman AB, Cherala G, Stanczyk FZ. Metabolism and pharmacokinetics of contraceptive steroids in obese women: a review. Contraception 2010;82: 314–23.

19. Goldzieher JW, Stanczyk FZ. Oral contraceptives and individual variability of circulating levels of ethinyl estradiol and progestins. Contraception 2008;78: 4–9.

20. Stanczyk FZ. All progestins are not created equal. Steroids 2003;68:879–90.

21. Odlind V. Can changes in sex hormone binding globulin predict the risk of venous thromboembolism with combined oral contraceptive pills? Acta Obstet Gynecol Scand 2002;81:482–90.

22. Jensen JT, Burke AE, Barnhart KT, Tillotson C, Messerle-Forbes M, Peters D. Effects of switching from oral to transdermal or transvaginal contraception on markers of thrombosis. Contraception 2008;78:1–8.

23. Edelman AB, Cherala G, Munar MY, DuBois B, McInnis M, Stanczyk FZ, et al. Prolonged monitoring of ethinyl estradiol and levonorgestrel levels confirms an altered pharmacokinetic profile in obese oral contraceptives users. Contraception 2013;87:220–6.

24. Simmons K, Edelman A. Obesity and bariatric surgery. In: Cwiak C, Allen RH, editors. Contraception for the medically challenging patient. New York: Springer; 2014:157–80.

25. Mornar S, Chandra A, Mistretta S, Neustadt A, Martinez G, Gilliam M. Pharmacokinetics of the etonogestrel contraceptive implant in obese women. Am J Obstet Gynecol 2012;207:110.e1–6.

26. Morrell KM, Cremers S, Westhoff C, Davis AR. Etonogestrel levels in normal-weight, overweight and obese women after 1 year or more of contraceptive implant use. Contraception 2014;90:292–3.

27. McNicholas C, Maddipati R, Zhao Q, Swor E, Peipert JF. Use of the etonogestrel implant and levonorgestrel intrauterine device beyond the U.S. Food and Drug Administration–approved duration. Obstet Gynecol 2015;125:599–604.

28. Westhoff CL, Torgal AH, Mayeda ER, Petrie K, Thomas T, Dragoman M, et al. Pharmacokinetics and ovarian suppression during use of a contraceptive vaginal ring in normal-weight and obese women. Am J Obstet Gynecol 2012;207:39.e1–6.

29. Smit J, Botha J, McFadyen L, Beksinska M. Serum medroxyprogesterone acetate levels in new and repeat users of depot medroxyprogesterone acetate at the end of the dosing interval. Contraception 2004;69:3–7.

30. Fotherby K, Koetsawang S. Metabolism of injectable formulations of contraceptive steroids in obese and thin women. Contraception 1982;26:51–8.

31. Jain J, Jakimiuk AJ, Bode FR, Ross D, Kaunitz AM. Contraceptive efficacy and safety of DMPA-SC. Contraception 2004;70:269–75.

32. Zieman M, Guillebaud J, Weisberg E, Shangold G, Fisher AC, Creasy G. Contraceptive efficacy and cycle control with the Ortho Evra/Evra transdermal system: the analysis of pooled data. Fertil Steril 2002;77(2 Suppl 2):S13–8.

33. Seeber B, Ziehr SC, Gschließer A, Moser C, Mattle V, Seger C, et al. Quantitative levonorgestrel plasma level measurements in patients with regular and prolonged use of the levonorgestrel-releasing intrauterine system. Contraception 2012;86:345–9.

34. Lopez LM, Grimes DA, Chen M, Otterness C, Westhoff C, Edelman A, et al. Hormonal contraceptives for contraception in overweight or obese women. Cochrane Database Syst Rev 2013:CD008452.

35. Holt V, Cushing-Haugen K, Daling J. Body weight and risk of oral contraceptive failure. Obstet Gynecol 2002;99:820–7.

36. Holt VL, Scholes D, Wicklund KG, Cushing-Haugen KL, Daling JR. Body mass index, weight, and oral contraceptive failure risk. Obstet Gynecol 2005;105: 46–52.

37. Brunner Huber LR, Hogue C, Stein A, Drews C, Zieman M. Body mass index and risk for oral contraceptive failure: a case–cohort study in South Carolina. Ann Epidemiol 2006;16:637–43.

38. Schramm GA, Schrah G. The efficacy and safety of an oral contraceptive containing chlormadinone acetate: results of a pooled analysis of non-interventional trials in adult and adolescent women. Contraception 2011; 84:390–401.

39. Nakajima ST, Pappadakis J, Archer DF. Body mass index does not affect the efficacy or bleeding profile during use of an ultra-low-dose combined oral contraceptive. Contraception 2016;93:52–7.

40. Westhoff CL, Hait HI, Reape KZ. Body weight does not impact pregnancy rates during use of a low-dose extended-regimen 91-day oral contraceptive. Contraception 2012;85:235–9.

41. Burkman RT, Fisher AC, Wan GJ, Barnowski CE, LaGuardia KD. Association between efficacy and body weight or body mass index for two low-dose oral contraceptives. Contraception 2009;79:424–7.

42. Yamazaki M, Dwyer K, Sobhan M, Davis D, Kim MJ, Soule L, et al. Effect of obesity on the effectiveness of hormonal contraceptives: an individual participant data meta-analysis. Contraception 2015;92:445–52.

43. Dinger JC, Cronin M, Möhner S, Schellschmidt I, Minh TD, Westhoff C. Oral contraceptive effectiveness according to body mass index, weight, age, and other factors. Am J Obstet Gynecol 2009;201:263.e1–9.

44. Vessey M, Painter R. Oral contraceptive failures and body weight: findings in a large cohort study. J Fam Plann Reprod Health Care 2001;27:90–1.

45. Dinger J, Do Minh T, Buttmann N, Bardenheuer K. Effectiveness of oral contraceptive pills in a large U.S. cohort comparing progestogen and regimen. Obstet Gynecol 2011;117:33–40.

46. Westhoff C. Higher body weight does not affect NuvaRing's efficacy [abstract]. Obstet Gynecol 2005;105:56S.

47. Xu H, Wade JA, Peipert JF, Zhao Q, Madden T, Secura GM. Contraceptive failure rates of etonogestrel subdermal implants in overweight and obese women. Obstet Gynecol 2012;120:21–6.

48. Benagiano G, Diczfalusy E, Goldzieher JW, Gray R. Multinational comparitive clinical evaluation of two long-acting contraceptive steroids: norethisterone oenanthate and medroxyprogesterone acetate. Contraception 1977; 15:513–33.

49. Jatlaoui TC, Curtis KM. Safety and effectiveness data for emergency contraceptive pills among women with obesity: a systematic review. Contraception 2016; http://dx.doi.org/10.1016/j.contraception.2016.05.002 [Epub ahead of print].

50. Edelman AB, Cherala G, Blue SW, Erikson DW, Jensen JT. Impact of obesity on the pharmacokinetics of levonorgestrel-based emergency contraception: single and double dosing. Contraception 2016;94:52–7.

51. Turok DK, Jacobson JC, Dermish AI, Simonsen SE, Gurtcheff S, McFadden M, et al. Emergency contraception with a copper IUD or oral levonorgestrel: an observational study of 1-year pregnancy rates. Contraception 2014;89:222–8.

52. Grimes DA, Shields WC. Family planning for obese women: challenges and opportunities. Contraception 2005;72:1–4.

53. World Health Organization. Medical eligibility criteria for contraceptive use. Geneva: WHO; 2015.

54. Centers for Disease Control and Prevention. U.S. medical eligibility criteria for contraceptive use, 2010. MMWR Recomm Rep 2010;59: 1–86.

55. Horton LG, Simmons KB, Curtis KM. Combined hormonal contraceptive use among obese women and risk for cardiovascular events: a systematic review. Contraception 2016; http://dx.doi.org/10.1016/j.contraception.2016.05.014 [Epub ahead of print].

56. Lidegaard O, Lokkegaard E, Jensen A, Skovlund C, Keiding N. Thrombotic stroke and myocardial infarction with hormonal contraception. N Engl J Med 2012;366:2257–66.

57. Schwartz S, Petitti D, Siscovick D, Longstreth W, Sidney S, Raghunathan T, et al. Stroke and use of low-dose oral contraceptives in young women. Stroke 1998;29:2277–84.

58. de Bastos M, Stegeman BH, Rosendaal FR, Van Hylckama Vlieg A, Helmerhorst FM, Stijnen T, et al. Combined oral contraceptives: venous thrombosis. Chichester, United Kingdom: John Wiley & Sons; 1996.

59. Manzoli L, de Vito C, Marzuillo C, Boccia A, Villari P. Oral contraceptives and venous thromboembolism. Drug Saf 2012;35:191–205.

60. Pomp E, Lenselink A, Rosendaal FR, Doggen CJM. Pregnancy, the post-partum period and prothrombotic defects: risk of venous thrombosis in the MEGA study. J Thromb Haemost 2008;6:632–7.