

Update on Hormonal Contraception and Obesity

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Abstract As the prevalence of obesity increases among women of reproductive age, providers must be aware of the safe and effective contraceptive methods available to reduce the adverse consequences of unintended pregnancy in this population. Hormonal contraception, in particular, has potential for increased risk in obese women. In addition, some pharmacokinetic studies suggest that contraceptive efficacy may be compromised in obese women. This review summarizes the known potential risks and variations in efficacy for hormonal contraception in obese and overweight women and in women following bariatric surgery.

Keywords Obesity · Body mass index (BMI) · Contraception · Bariatric surgery · Efficacy · Safety

Introduction

Obesity and unintended pregnancy have reached epidemic levels as issues impacting the health of women and their families. Worldwide, over 1.4 billion people are overweight (defined as having a body mass index (BMI) ≥ 25 kg/m²) and over 500 million people are obese (defined as BMI ≥ 30 kg/m²) [1].

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Specifically in the United States (US), 66 % of adult women are overweight or obese and 36 % are obese. Over one third of female teens are overweight or obese and one in five is obese. [2] The prevalence of unintended pregnancy rivals that of obesity. Worldwide, there are 85 million unintended pregnancies per year, representing 40 % of all pregnancies. [3] In the US, nearly half of all pregnancies are unintended [4].

Safe and effective contraception is of paramount importance for overweight and obese women, as these women are at higher risk of pregnancy-related complications such as gestational diabetes, preeclampsia, cesarean delivery, fetal anomalies, and stillbirth [5–10]. Furthermore, overweight and obese women may be at increased risk of unintended pregnancy. While it is true that obesity can contribute to anovulation and resulting impairment of fertility, the majority of obese women, like their normal BMI counterparts, ovulate regularly [5]. Obese women often have a longer fertility window owing to earlier ages of menarche associated with adolescent obesity. [11]. In addition, while overweight and obese women engage in similar sexual behaviors that put them at risk for pregnancy, multiple studies have shown that obese women are less likely to initiate and effectively use contraception [12–16].

Concerns about hormonal contraceptive use in women with a higher BMI are based on the potential for decreased efficacy and increased medical risk [17]. However, obese women have traditionally been excluded from clinical contraception trials [5, 7]. Increasing attention to the interaction between obesity and hormonal contraception is evident by the growing number of publications, and this review will focus on recent updates and briefly review the older literature.

Safety of Hormonal Contraceptive Use in Obese Women

As in the non-obese population, the risks of pregnancy in obese women are generally higher than the risks associated

with use of hormonal contraception [18]. The U.S. Medical Eligibility Criteria for Contraceptive Use (US MEC) classifies all contraceptive methods for otherwise healthy women with obesity as category 1 (no restriction for use), except for combined hormonal methods (pill/patch/ring) that are category 2 (advantages generally outweigh the risks). This difference exists for obese women due to the increased risk of thromboembolism with estrogen-containing methods. For obese adolescents, progestin injections are assigned a category 2 given the possible association with additional weight gain [19••]. Of note, these risk estimates are compared to unplanned pregnancy and one should consider risks carefully when using hormonal contraceptives to treat other conditions.

Venous Thromboembolism

One of the major safety concerns associated with hormonal contraception is the risk for venous thromboembolism (VTE). While it is well accepted that the use of low dose estrogen-containing combined oral contraceptives (COCs) slightly increases the incidence of VTE (5–10 cases in non-users vs. 15–30 cases in users per 10,000 women per year) and that obesity also increases the risk of VTE, less is known about the precise interaction between these two factors [5]. A large 2002 Dutch case control study suggested no increased VTE risk associated with obesity among COC users, however, more recent studies have consistently shown a significant interaction between obesity and COC use [20–24]. A study by Pomp et. al. published in 2007 reported a 2.5- and 3.0-fold increased risk of VTE among overweight and obese non-COC users compared to normal BMI non-users. Furthermore, overweight and obese COC users had a 12- and 24-fold increased risk of VTE compared to normal BMI non-users [23]. Though there has been conflicting evidence suggesting an increased risk of VTE associated with contraceptive patch use, there are no published studies focusing on VTE risk in obese patch users [5].

Body Weight

In addition to thromboembolism, the fear of additional weight gain is a common concern when discussing hormonal contraceptives with patients. Weight gain is a frequently reported side effect of hormonal contraceptives [25–28] and a reason for discontinuation [29, 30]. Though a causal relationship has not definitively been established, some older research has suggested that intramuscular (IM) depot medroxyprogesterone acetate (DMPA) injection may be associated with increased weight gain in obese adolescents [31–33]. However, other than the specific population of

obese adolescents, numerous studies confirm no relationship between hormonal contraceptives and weight gain in the general population. There is limited information about the effect of hormonal contraceptives on weight change in overweight and obese women who were traditionally excluded from earlier studies [5, 33, 34•]. Available research on the effect of hormonal contraceptives on weight gain in the obese population is limited to DMPA and oral contraceptives. Mayeda et. al. recently published a planned secondary analysis of a prospective study of normal-weight women ($n=96$) and obese women ($n=54$) randomized to 3–4 months of 30 μg ethinyl estradiol (EE)/150 μg levonorgestrel (LNG) or 20 μg EE/100 μg LNG COC to evaluate weight and body composition. They found that neither COC formulation was associated with short term weight gain, or with changes in body composition (as measured by total body water, percent body fat, fat mass, and fat free mass) in either normal-weight or obese women [34•].

Metabolic Health

Several recent studies have examined the effect of hormonal contraceptives on metabolic health parameters in obese women. A 2012 prospective study evaluated changes in carbohydrate and lipid parameters over 3 months of COC use with either 30 μg EE/150 μg LNG vs 20 μg EE/100 μg LNG. They found that obesity had little effect on COC-induced changes in carbohydrate and lipid metabolism. Normal-weight ($n=71$) and obese participants ($n=28$) experienced similar minor metabolic changes, with the exception of LDL alterations. The mean LDL rose 3.8 mg/dl (± 17.3) in normal-weight participants, whereas it fell 4.9 mg/dL (± 20.6) in the obese group ($p=0.02$). The only difference related to COC dosing was a marginally significant increase in glucose levels among obese subjects using the higher dose COC ($p=0.06$). This study confirms previous findings showing COCs induce small, but not necessarily clinically significant, changes in carbohydrate and lipid metabolism in normal-weight women and extends these results to obese women [35•]. While this data on COC use is reassuring, other research suggests a potential deleterious effect of DMPA use on glucose regulation in obese women. Specifically, a prospective study of subcutaneous DMPA (DMPA-SC) on cardiometabolic markers in obese ($n=10$) and normal-weight women ($n=5$) followed over 18 weeks found that obese women had a significantly greater decline in beta-cell compensation for insulin resistance after initiating DMPA-SC. In addition, obese DMPA-SC users had an increased cardiometabolic risk at baseline as evidenced by body morphology, HDL cholesterol, triglycerides, insulin sensitivity, and acute insulin response to glucose [36•].

Bone Health

DMPA is known to cause temporary reversible bone loss in women, but there is very limited evidence about bone loss differences associated with BMI in DMPA users. A pilot study ($n=15$) of short term changes in bone mineral density associated with subcutaneous DMPA showed no significant difference over 18 weeks in lumbar spine bone mineral density in the different BMI classes (normal BMI, class 1-2 obesity, or class 3 obesity) [37]. Moreover, obese women are generally at low risk for osteoporotic fracture given the protective effect of obesity on bone mineral density [38].

Benefits of Hormonal Contraceptive Use in Obese Women

In addition to pregnancy prevention, hormonal contraceptives offer several other benefits specific to obese women. Most notably, hormonal contraception usage has the potential to reduce the risk of endometrial cancer. Given that obesity is an independent risk factor for endometrial cancer, hormonal contraceptives may have an added benefit for obese women by providing protection from endometrial cancer [5]. Hormonal contraceptives may also be used for cycle regulation and management of anovulation.

Contraceptive Efficacy in Obese Women, by Method

Currently, the US MEC does not advise varying hormonal contraception prescriptions for obese women on the basis of concern for decreased efficacy, except in cases of women having had malabsorptive bariatric surgery, as described below [19••]. There is some evidence available specific to the efficacy of various hormonal methods of contraception in overweight women compared to normal-weight women. Most of these studies, however, are limited by small sample size or by study design. In addition, the differences in efficacy described in the available literature may be attributable to confounding factors such as compliance.

- Combined Oral Contraceptive Pills/Contraceptive Ring/Contraceptive Patch

Combined oral contraceptive pills (COCs), which function to suppress ovulation, remain the most common contraceptive method of choice among reproductive age women in the US. In 2009, Trussell and colleagues published a summary of eight studies on the relationship between obesity and COC failure. They concluded that, compared to normal-weight women, there is no convincing evidence that obese women have increased risk of method failure with COCs, even with lower dose formulations, when studies adjusted for duration of use,

socioeconomic factors, parity, and self-reported use of dual methods [39]. Two studies measuring COC pharmacokinetics and ovarian follicular development in obese and non-obese women found no difference in follicular activity despite some differences in serum levels. Therefore, if some studies suggest a difference in failure related to weight, the failures are likely not related solely to differences in ovarian suppression [13, 40].

Trussell comments that since most contraceptive failures are associated with incorrect usage, and since studies inconsistently measure weight at the actual time of an unplanned pregnancy, there are limitations to most reports examining differences in method-related efficacy among obese and non-obese COC users. It is possible that COC failure in obese women is more sensitive to incorrect usage as BMI increases [39]. To further complicate the ability to estimate failure rates, a 2012 report by Westhoff identified that obese women had higher rates of noncompliance with COC use, as measured by serum LNG levels (OR 2.8, 95 % CI 1.2-6.8) [14].

Differences in COC dose and in cyclic, extended cycle, or continuous administration may impact efficacy for obese women more than non-obese controls. A comparison of women using a standard 21-day or 24-day regimen of various COCs reported a higher overall efficacy of the 24-day regimen even in women with a BMI ≥ 25 kg/m², but with a slight reduction in efficacy in both groups as BMI increased [41]. This analysis by Dinger et al. included 73,269 woman-years of COC exposure but did not report the proportion of women in higher BMI categories. They calculated a contraceptive failure hazard ratio of 1.5 (95 % CI 1.3-1.8) in women with a BMI ≥ 35 kg/m² compared to those with a BMI less than 35 kg/m².

Another recent study demonstrated improved, but not complete, suppression of follicular activity in obese women continuously administered 20 mcg of EE/LNG, or cyclically administered 30 mcg EE/LNG COCs, compared to the follicular activity seen with use of cyclically administered 20 mcg COCs [42•]. However, in a clinical trial evaluating efficacy of an extended cycle formulation of 20 mcg EE and LNG which included 1,736 women, 50.6 % of whom were above a BMI of 35 kg/m², there were no differences in crude pregnancy rates when stratified by weight or BMI [43••]. This publication is remarkable for being one of the largest modern clinical trials of contraceptive efficacy that did not restrict enrollment based on weight or BMI, resulting in a high proportion of overweight women available for analysis.

For other delivery systems of combined hormonal contraception, the evidence is mixed. A 2013 study monitored serum hormone levels and ovarian follicular activity in women using the EE/Etonogestrel (ENG) vaginal ring. No differences were seen, supporting comparable efficacy of the contraceptive ring in obese and non-obese women, even with up to 42 days of continuous use [44•]. A pooled analysis of clinical trial results for the contraceptive patch containing norelgestromin/EE

reported higher failure rates for subjects in the top decile by body weight (>198 lb) and this warning remains on the current package labeling [45, 46]. However, two recent studies of contraceptive patches in development (containing EE and gestodene or LNG) included higher proportions of obese participants in their clinical trials, and both reports demonstrate no increase in failure rate among obese subjects despite lower EE doses [47, 48]. Finally, McNicholas et al. reported no difference in failure rates across BMI categories among a combined population of COC, patch, and ring users over three years while enrolled in the Contraceptive CHOICE Project [49]. This prospective trial adds support for the conclusion that combined contraceptive methods should be regarded as highly effective for both obese and non-obese women when used correctly. However, the similar efficacy may be explained by inadequate power to detect a difference, especially if this report had separately analyzed users of the patch, ring, or pill by dose or regimen. [50].

- Progestin-only pills

Re-analysis of a large prospective study in the United Kingdom initially published in 1990 determined no statistical difference in failure rate between women 82 kg (180 lb) or more and normal-weight women using progestin-only pills (POPs). However, the study was under-powered to detect this difference as only 1 of the total 38 pregnancies during POP use was in a woman reported to weigh over 77 kg (177 lb). The failure rate for all women using POPs was reported as 38 “accidental” pregnancies in 6,779 woman-years of use (0.56 per 100). When compared to other methods and to the 95 pregnancies in 48,692 women-years of COC use in this population (0.20 per 100), POPs appear to have a very high overall efficacy [51]. Both of these pregnancy rates are lower than those reported in clinical trials of modern oral contraceptives, despite minimal loss to follow-up, suggesting that this result cannot be generalized. There are no more recent studies available to confirm these findings.

- Progestin-only Injection and Implant

Several studies have demonstrated that IM DMPA effectively suppresses ovulation in overweight women. DMPA-SC was more recently studied in normal, Class 1-2 obese (BMI 30-39.9 kg/m²) and Class 3 obese (BMI ≥40 kg/m²) women with no evidence of ovulation reported in any group except in the first week following the initial injection. Serum levels of DMPA were lower overall in women at higher BMI categories, but remained above the defined contraceptive threshold [52]. The clinical trials for the ENG contraceptive implant excluded women above 130 % of ideal body weight, prompting an initial caution regarding

unknown efficacy in this population. A pharmacokinetic study of ENG levels over six months in obese women with the implant found consistently lower serum values compared to normal-weight women. Extrapolating the results over time to two or three years following insertion, the estimated serum levels are very close to the cut-off commonly believed to provide suppression of ovulation [53]. However, recently presented data from ENG implant users demonstrated that serum levels of ENG remained above the threshold required for contraceptive efficacy across BMI categories, even after three years of use [54]. Finally, Xu and colleagues recently reported results for women selecting the ENG implant as part of the Contraceptive CHOICE Project. They found no reduction in efficacy for the implant in overweight or obese women compared to normal-weight participants [55].

- Levonorgestrel intrauterine device (IUD)

Both hormonal and non-hormonal IUDs are thought to be highly effective for women regardless of weight or BMI. IUD insertion can be more difficult in obese patients, and ultrasound guidance may be helpful for some obese patients [56]. One study showed lower LNG serum levels in a small population of women with a BMI >30 kg/m² as compared to LNG IUD users at lower BMIs; however, the contraceptive mechanism of the LNG IUD depends on local effects, not serum levels [57].

- Emergency Contraception

Two randomized controlled trials have compared LNG and ulipristal acetate (UPA) for emergency contraception (EC). A meta-analysis of these trials calculated a greater than 3-fold risk of failure for EC in women with a BMI ≥25 kg/m² (or 165 lbs) compared to normal-weight women. The risk was higher for obese women following use of LNG (OR 4.42) compared to UPA (OR 2.62). In fact, there was demonstrated to be minimal reduction in pregnancy rates as weight increased, suggesting no benefit for use of LNG for EC in women over 77 kg, nor for UPA in women over 88 kg [58•]. A pooled analysis of pregnancy rates following use of UPA for EC reported that obese women were twice as likely to experience pregnancy compared to non-obese women [59]. There is also no evidence that doubling or increasing the dose of EC in obese women is a more effective regimen, and the safety of this dosage is unknown. A copper IUD should be considered as a first line option in women of any weight requesting EC. In women who do not desire IUD placement, UPA is superior to LNG for EC in women with a BMI ≥25 kg/m² (or 165 lbs) [58•]. If UPA is unavailable and an IUD is not desired, the data suggest that LNG has no reduction in pregnancy rates for women over 77 kg.

Bariatric Surgery

Bariatric surgery has become increasingly common, especially in women. Women comprised 79 % of the 125,000 procedures performed annually between 2003 and 2008 in the US [60]. Between 1998 and 2005, 83 % of bariatric procedures on reproductive age individuals were performed in women [61]. In addition to concerns about hormonal contraception for obese women already addressed, female bariatric patients face additional issues with regard to hormonal contraception efficacy and safety.

Effective contraception is particularly important to address for bariatric surgery patients, as there may be a rapid return to fertility with weight loss from the procedure. Because of the potential complications of an unintended pregnancy in the immediate post-operative period, the American Association of Metabolic and Bariatric Surgery (ASMBS), the American Association of Clinical Endocrinologists (AACE), and the Obesity Society (TOS) recommend avoiding pregnancy for 12 to 18 months after bariatric surgery [62]. Despite this recommendation, there is limited and inconsistent evidence about hormonal contraceptive efficacy in bariatric surgery patients. Because of the risk of impaired absorption of oral contraceptives following malabsorptive bariatric surgeries (including Roux-en-Y gastric bypass which accounts for 47 % of all bariatric surgeries), the US MEC classifies all oral contraceptives (COCs and POPs) as category 3 in the bariatric population [19•, 63]. Though the rationale for this recommendation makes intuitive sense, there is limited supporting evidence. While a few small observational and pharmacologic studies have suggested higher oral contraceptive failure and/or lower plasma contraceptive levels, others found contrary results [64–66]. Moreover, these studies were all limited to jejunoileal bypass – a restrictive bariatric procedure that is no longer commonly used [67]. Another observational study examining oral contraception effectiveness following gastric banding identified no pregnancies among an unspecified number of oral contraceptive users over two years [68].

Even less is known about non-oral hormonal contraceptive use among bariatric surgery patients. A small case series by Ciangura et al. examined ENG concentrations in three women with pre-operatively placed ENG-releasing implants who underwent Roux-en-Y gastric bypass. They found that ENG levels decreased over time with weight loss, but remained above the minimum concentration (90 pg/mL) required for effective contraception at eight months following insertion [69]. Another recent study examining the acceptability of the LNG IUD among adolescent bariatric surgery patients observed no failures within 6 months among the 23 adolescents who had an LNG IUD placed at the time of bariatric surgery [70].

Though we know that the risks of hormonal contraception use in bariatric surgery patients are generally exceeded by the risks associated with pregnancy, similar to the general

population, further research is needed to better understand the specific risks and efficacy of hormonal contraception in the rapidly growing female bariatric surgery population [71]. Currently, the US MEC supports the use of all hormonal contraceptive methods for women who have undergone restrictive bariatric surgery (category 1) and all non-oral methods for women who have undergone malabsorptive bariatric procedures (category 1).

Conclusion

Given the growing obesity epidemic and the pregnancy-related risks associated with obesity, safe and effective contraception is of paramount importance for overweight and obese women at risk for unintended pregnancy. Though data on this subject are limited due to routine exclusion of obese women from clinical hormonal contraception trials in the past, there has been a growing amount of research on hormonal contraception for overweight and obese women in the last several years. The following conclusions and recommendations are based on the available evidence described above:

- Safety
 - As in the non-obese population, the risks of hormonal contraception use in obese women are generally exceeded by the risks associated with pregnancy [18].
 - Long-acting reversible contraceptives, including IUDs and implants, are generally regarded as safe for obese women.
 - Estrogen-containing methods, including COCs, the ring, or patch (US MEC category 2), are associated with an increased risk of VTE, although the absolute risk remains low for most women.
 - Though there is some evidence to suggest an increased risk of weight gain in adolescent DMPA users (US MEC category 2), there is no evidence to support a causal relationship between other hormonal contraceptives and weight gain in obese women [5, 19•, 33, 34•].
 - COCs and DMPA may be associated with changes in cardiometabolic markers in obese women, but the clinical importance is unknown [35•, 36•].
 - The effects of DMPA on bone health are similar in obese and normal-weight women [37].
- Efficacy
 - The contraceptive vaginal ring, DMPA, and IUDs have comparable efficacy in obese and non-obese women [44•, 49, 56].
 - Any measurable difference in efficacy of COCs between obese and non-obese women may be attributable to

differences in compliance, and is likely not clinically significant enough to warrant routine non-prescription of COCs for this reason alone [39]. To improve efficacy for obese patients, one must consider prescribing continuous use of 20 mcg of COCs, or increasing the dose to a cyclic 30 mcg of COC [42•].

- Pharmacokinetic studies with the ENG contraceptive implant suggest there may be decreased serum levels of ENG in obese women; however, there is good evidence for levels sufficient to suppress ovulation in users across BMI categories, even with up to three years of use [53, 54]. A prospective study supports comparable efficacy in obese and non-obese women with follow-up over three years [55].
- The copper IUD is a highly-effective non-hormonal option for EC that should be offered as a first-line therapy, especially in obese women. In women who do not desire IUD placement, UPA is superior to LNG for EC in women with a BMI ≥ 25 (or 165 lbs) [58•, 59].
- ENG implants and LNG IUDs appear to be an effective and well tolerated option for women who have undergone bariatric surgery.
- Given the theoretical potential for decreased efficacy due to malabsorption, all oral contraceptives, including COCs and POPs, are classified as category 3 by the US MEC for women who have undergone malabsorptive bariatric procedures [19••]. However, there is limited conflicted research to support this recommendation [64–66, 68].

Compliance with Ethics Guidelines

Conflict of Interest Katherine D. Pocius and Caryn R. Dutton declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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