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Obesity and hormonal contraceptive efficacy

Jennifer A Robinson, MD, MPH[*,1] and **Anne E Burke, MD, MPH**[1]

[1]Department of Gynecology & Obstetrics, Johns Hopkins University Bayview Medical Center, 4940 Eastern Avenue, A Building, Room 121, Baltimore, MD 21224, USA

Abstract

Obesity is a major public health concern affecting an increasing proportion of reproductive-aged women. Avoiding unintended pregnancy is of major importance, given the increased risks associated with pregnancy, but obesity may affect the efficacy of hormonal contraceptives by altering how these drugs are absorbed, distributed, metabolized or eliminated. Limited data suggest that long-acting, reversible contraceptives maintain excellent efficacy in obese women. Some studies demonstrating altered pharmacokinetic parameters and increased failure rates with combined oral contraceptives, the contraceptive patch and emergency contraceptive pills suggest decreased efficacy of these methods. It is unclear whether bariatric surgery affects hormonal contraceptive efficacy. Obese women should be offered the full range of contraceptive options, with counseling that balances the risks and benefits of each method, including the risk of unintended pregnancy.

Keywords

birth control; hormonal contraception; obesity; pharmacodynamics; pharmacokinetics

Obesity and being overweight represent one of the largest preventable health conditions, affecting 1.4 billion adults globally, including nearly 300 million obese women [101]. Obesity is associated with adverse health effects, such as hypertension, hyperlipidemia and Type II diabetes. For women of reproductive age, obesity confers additional risks during pregnancy, such as increased rates of spontaneous abortion, pre-eclampsia, gestational diabetes, shoulder dystocia and cesarean section [1]. Thus, preventing unintended pregnancy

[*]Author for correspondence: Tel.: +1 410 550 0336 jrobin87@jhmi.edu.

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CME Author
Charles P Vega, MD, Associate Professor and Residency Director, Department of Family Medicine, University of California, Irvine, CA, USA
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is at least as important for obese women, as for women contending with any chronic health condition.

There are many ways to quantify obesity, the most common being the BMI (BMI = weight in kilograms divided by the square of height in meters). BMI provides a continuous measurement of weight-for-height, with cutoffs for overweight and different classes of obesity as presented in Table 1 [2]. Class 1 obesity is considered to be moderate, class 2 severe and class 3 is considered as morbid obesity.

Obese individuals experience a number of physiologic changes compared with normal-weight individuals, ranging from an increase in cardiac output to alterations in liver enzyme function [3]. Some of these alterations have the potential to affect how drugs are absorbed, distributed, metabolized and eliminated. Changes in any of these processes may affect the efficacy of a drug. There is concern that the efficacy of hormonal contraception in obese women may be adversely affected for these reasons.

In order to understand the potential impact that obesity may have on contraceptive efficacy, we review some basic concepts of pharmacokinetics (PK), and briefly discuss how obesity might affect PK parameters. We then review available evidence for the efficacy of specific contraceptive methods in obese women. While efficacy is a separate concern from safety, concerns for adverse effects may limit providers' willingness to provide certain contraceptives to obese women. Therefore, a brief discussion of contraceptive safety in obese women is included in this review. Finally, we discuss the use of contraceptives in women who have had bariatric surgery, an increasingly common treatment for obesity among women of reproductive age.

PK implications: cause for concern?

PK refers to the study of how drugs move through the body, encompassing how a drug is absorbed, distributed, metabolized and eliminated [4]. Important PK parameters, which are used to quantify these attributes are calculated from the drug's concentrations in blood. Such parameters include bioavailability, volume of distribution (Vd), clearance, half-life (t½), area under concentration time-curve (AUC) and the minimum and maximum serum concentrations (C_{min} and C_{max}, respectively). A drug's efficacy is very often a function of one or more of its PK parameters [5]. The PK parameters that are most relevant for efficacy of contraceptive steroids are uncertain. Obesity itself causes a number of physiologic and metabolic changes that may affect PK parameters of systemically administered drugs. Whether or not this subsequently affects contraceptive efficacy is not certain, but an effect is believed to be plausible [6].

Absorption

Drug absorption depends on multiple factors, including a drug's dose and route of administration. Absorption influences a drug's bio-availability, or the amount absorbed into the systemic circulation. Drugs that are administered intravenously have 100% bioavailability, since they are immediately delivered into the circulation. The bioavailability of orally dosed drugs, on the other hand, depends on how efficiently the compound is

absorbed through the gut, as well as how much is metabolized by the gastrointestinal epithelium or the liver. For instance, an intravenous dose of ethinyl estradiol (EE) has a bioavailability of 100%, while the same dose given orally has a bioavailability of only 44% [7]. Oral drugs enter the portal (hepatic) circulation after they are absorbed by the gut. The hepatic metabolism that occurs before the drug reaches the systemic circulation is referred to as first-pass metabolism; this can greatly affect the proportion of the drug that is available to exert its therapeutic effect. Alternate dosing routes, such as transdermal, transvaginal or intramuscular, avoid first-pass metabolism and can improve the drug's bioavailability compared with oral dosing.

Obese individuals may have increased absorption through the gut due to increased gut perfusion (a result of increased cardiac output) and increased gastric emptying time [7]. A drug that is delivered transdermally or intramuscularly may exhibit slower absorption in the presence of increased fat deposits. Both of these changes can affect bioavailability. Little is known about whether obesity affects the absorption of parenteral drugs.

Distribution

After absorption, a drug is dispersed throughout the body into various compartments depending on its chemical properties, such as size, charge, lipophilicity or affinity for plasma proteins. These factors influence the drug's Vd, the apparent space in the body that the drug can occupy. The total exposure to a drug is measured by the AUC, which is calculated from serial serum concentrations drawn at multiple time points. Those concentrations can also be used to determine C_{min} and C_{max} after a single dose of the drug. Obesity may alter Vd through changes in plasma proteins that can either increase or decrease the amount of drug that is protein-bound. Since the unbound fraction of drug exerts the therapeutic effect, changes in protein binding can alter the drug's activity [5].

Metabolism

The effects of obesity on drug metabolism are unclear. Obesity is associated with fatty infiltration of the liver, which can lead to global liver dysfunction and reduced enzyme activity, especially in the morbidly obese [3]. It is also associated with decreased activity of the hepatic enzyme CYP3A4, the enzyme primarily responsible for metabolism of contraceptive steroids [7]. Adipose tissue may also have some intrinsic metabolic activity, which could affect hormonal contraceptives.

Elimination

Clearance refers to how quickly the body can eliminate the drug, usually via the kidneys or liver. A drug's t½ refers to the time required for the drug's concentration to be reduced by half, and this parameter is a function of both Vd and clearance. The t½ influences the time needed for the drug to reach steady-state concentration, which typically requires four to five half-lives [8]. The rate of drug elimination may be increased due to obesity-related increases in renal clearance [7]. However, the increased clearance may not lead to changes in the drug's t½ if it is offset by an increase in Vd [3]. Drugs that are lipophilic may have decreased clearance in obese women, if the drug experiences slower release from fat than other tissues [7].

Pharmacodynamics

The effects a drug has on a body's functions, known as pharmacodynamics, are the main reason to be concerned about PK alterations. Examples of contraceptive pharmacodynamic outcomes are suppression of ovarian follicular development, alterations in characteristics of cervical mucus or hormonal effects on the endometrium. It is generally accepted that PK influence pharmacodynamic findings, although the exact relationships between PK and pharmacodynamics may not be entirely clear. This seems to be especially true for contraceptive hormones, for which there can be large intra-individual and interindividual variability in PK parameters, particularly for the hormones in oral contraceptives [9]. This variability may account for differing responses to a given contraceptive, such as bleeding patterns or contraceptive failure. Ultimately, the PK and pharmacodynamic ramifications of obesity and contraception remain poorly understood.

Efficacy of hormonal contraceptives among obese women

Much of the concern for altered hormonal contraceptive efficacy in obese women stems from worries about how weight-related physiologic alterations affect the PK of estrogenic and progestogenic contraceptive hormones, and whether this translates into altered pharmacodynamics. Below, available data about efficacy of common hormonal contraceptives when used by obese or overweight women are discussed.

Used correctly, modern contraceptives are very effective at preventing unintended pregnancy. Comparisons of perfect use and typical use estimates are presented in Table 2 [10]. Perfect use can be equated with efficacy – how well a given contraceptive can work, if used exactly as intended. Depending on user burden, typical-use failure rates (contraceptive effectiveness) may diverge significantly from perfect-use failure rates. Typical-use failure rates are generally affected by factors such as contraceptive compliance or adherence, whereas perfect-use failure rates (efficacy) reflect inherent properties of a method. No published studies clearly demonstrate that obese women are less likely than nonobese women to be compliant with a contraceptive method. Whether obesity has an impact on contraceptive efficacy is the concern that this article attempts to address.

Progestin-only contraceptives

Progestin-only contraceptives include long-acting reversible contraceptives (intrauterine devices [IUDs] and implants), injectables and progestin-only pills. The two available levonorgestrel (LNG)-releasing intrauterine systems (LNG-IUS) contain the progestin levonorgestrel and are highly effective at preventing pregnancy, one for 3 years, and one for at least 5 years [7]. The LNG-IUS delivers hormone directly to the endometrium where it leads to endometrial thinning and decidualization; ovulation may be suppressed in approximately half of cycles [11]. Progestin-only contraceptive implants deliver a continuous dose of progestin and prevent pregnancy for up to 3 years. Injectable progestins provide several weeks to months of contraceptive effect. Injectables and implants prevent pregnancy via ovulation suppression and progestin-mediated effects on the cervical mucus and endometrium.

Intrauterine devices

Owing to the contraceptive effect of IUDs occuring primarily via local actions on the uterus, there is no reason to think that IUDs would be less effective in obese women than in women of normal weight. There are few studies that evaluate differences in IUD contraceptive efficacy by weight. There are now two types of LNG-containing IUDs available in the USA. The more widely available device delivers 20 μg LNG/day for at least 5 years, and is likely to be effective for even longer. A newly-approved, slightly smaller IUD is intended to provide contraception for 3 years, with a lower release rate of LNG (14 μg/day). No data reporting differential efficacy by weight are available. The manufacturer reports that women with a BMI up to 55 kg/m^2 were enrolled in the clinical trial leading to US FDA approval, although the mean BMI was 25.3 kg/m^2 [12]. BMI was not reported for women who experienced the five pregnancies that occurred among 1432 participants in the first year of use.

An analysis of data from the Contraceptive CHOICE Project (a large, prospective study in St. Louis, MO, USA) that provided more than 9000 women with free contraception estimated the failure rate of the IUD (both the LNG-IUS and copper IUD) in obese and normal-weight women [13]. Over 4200 women received an IUD, the majority of whom selected the LNG-IUS [102]. A total of 12 pregnancies were observed among IUD users (five in normal weight, none in overweight and seven in obese women) over the course of 5985 woman-years of use. Failure rates for the IUD were less than one per 100 woman-years, and did not differ by BMI category. There are anecdotal reports of IUD insertion being more technically difficult in obese women, with theoretical concern for greater likelihood of expulsion, but published reports that address this issue are difficult to find.

Owing to its high efficacy, which is preserved across the BMI spectrum, intrauterine contraception is an excellent choice for obese women wishing to delay or avoid pregnancy.

Contraceptive implants

Etonogestrel implant—Prescribing information for the etonogestrel (ENG) implant indicates that serum ENG levels decline with increasing body weight [14]. Only one study directly measured the PK of the ENG contraceptive implant in obese women [15]. In comparing ENG concentrations in 13 obese women (BMI ≥30 kg/m^2) to four normal-weight women and historical controls, the authors found an almost 50% lower ENG AUC in the obese women compared with normal-weight women. They also estimated that obese women would experience 40% lower ENG exposure over the life of the implant. While none of the obese women were projected to have an ENG level below that which is believed to reliably suppress ovulation (90 pg/ml) [16], this study raised concerns that the implant may not be effective for the full 3 years in obese women.

Women who weighed greater than 130% of ideal body weight were generally excluded from efficacy studies of the ENG implant. A postmarketing study of 923 women using the ENG implant included 134 women who weighed more than 70 kg. These women contributed 218 woman-years of contraceptive use (only 4 woman-years of use for women >90 kg), and the authors reported that method failure rates were low and not affected by body weight [17].

Researchers at the Contraceptive CHOICE Project also estimated the failure rate of the ENG implant in obese and normal-weight women [13]. There was one pregnancy observed in an obese participant during 1377 women-years of implant use, for a cumulative failure rate among obese women of 0.23 per 100 woman-years. There was no significant difference in failure rates between the implant groups for any BMI category.

Finally, a 2011 case series reported the experiences of three morbidly obese women who had an ENG implant placed 1–2 months prior to undergoing Roux-en-Y gastric bypass surgery [18]. Serum ENG concentrations were measured prior to surgery, and 3 and 6 months after surgery. Two out of three women had lower pre-operative ENG concentrations than normal-weight historical controls, and all three women's ENG serum concentrations decreased at 3 and 6 months postoperatively. While all three had levels sufficient to prevent ovulation, the authors also raised concerns that the lower concentrations may indicate a need to replace the implant sooner than the licensed 3 years.

Levonorgestrel implants—While not currently available in the USA, several two-rod LNG implants are commonly used worldwide. Data on efficacy in obese women are sparse. One study comparing the two-rod LNG implant with the six-rod LNG implant (no longer used) enrolled 598 women, approximately 11% of whom had a body weight greater than 70 kg. Of the three recorded pregnancies in the LNG two-rod group, all were in women who weighed less than 70 kg. The authors concluded that body weight does not reduce the efficacy of the LNG implant [19].

In summary, the limited available published data on efficacy of progestin-only implants in obese women is reassuring. These highly effective, long-acting contraceptives may also be an excellent option.

Injectable contraception

Depot medroxyprogesterone acetate—Depot medroxyprogesterone acetate (DMPA) is an injectable contraceptive that is widely used around the world. It is provided as an intramuscular (im.) injection of 150 mg DMPA and provides highly effective, reversible contraception for approximately 3 months [20]. The efficacy of the intramuscular formulation is not known to be decreased in obese women. The subcutaneous (sc.) formulation (DMPA-sc.) delivers a lower dose of DMPA (104 mg) and provides comparable contraceptive effect.

A randomized, prospective, evaluator-blinded trial compared the effects of DMPA-im. to DMPA-sc. [21]. Women were followed through 3 months of a treatment cycle and until they resumed ovulation or up to 1 year after stopping the study drug. Results were stratified by BMI category, and no differences in PK parameters were found among different BMI categories. The mean trough concentration of medroxyprogesterone acetate was lowest in women with a BMI >30 kg/m^2, but was still above the threshold needed to suppress ovulation (200 pg/ml).

Another study evaluated the PK and pharmacodynamics of DMPA-sc. in women falling into three BMI categories: class 3 obese (BMI ≥40kg/m^2), class 1–2 obese (BMI 30–39.9

kg/m^2) and normal weight (BMI 18.5–24.9 kg/m^2) [22]. Serum medroxyprogesterone acetate concentrations were consistently lower in obese subjects than normal-weight subjects, but remained above the threshold needed for ovulation suppression. One participant with class 3 obesity became pregnant during the study, and it is believed that she conceived during the first week after DMPA-sc. administration, during which she did not use a back-up method as recommended. These studies suggest that obesity does not reduce the efficacy of DMPA. For use of the im. formulation, the depth of subcutaneous fat in some obese women may necessitate use of longer needles than those usually used for im. injections [23].

Norethisterone enanthate—Norethisterone enanthate is another injectable progesterone-only contraceptive method that is given every 8 weeks. It is not available in the USA, but is used in some other countries. A study comparing the PK of norethisterone enanthate in obese and normal-weight women found no difference in serum drug concentrations between the two groups [24]. We found no studies evaluating the efficacy of norethisterone enanthate in women in different weight categories.

Progestin-only pills

Progestin-only pills are seldom used by women in the USA [25]. There is a lack of data on differential contraceptive efficacy between obese and nonobese users of progestin-only pills.

Combined hormonal contraceptives

Combined oral contraceptive pills

The most common reversible contraceptive method in many markets is the combined oral contraceptive pill (COC) [103]. Since it became widely available in the 1960s, the dose of its component hormones has steadily decreased. Most available COCs contain EE as the estrogenic component. There are a variety of progestins in current formulations, and the progestin component is primarily responsible for the contraceptive effect. Progestins in sufficient doses suppress the hypothalamic–pituitary–ovarian axis leading to inhibition of ovulation. Secondary contraceptive effects include thickening of cervical mucus and thinning of the endometrial lining [26]. The estrogen component contributes to ovulation suppression and control of irregular bleeding. The transdermal patch and vaginal ring also contain a combination of estrogen and progestin. Their mechanism of action is the same as COCs.

Few studies investigate the effects of obesity on the PK of oral contraceptive steroids, although more studies are being carried out to address these concerns. We do know that COCs are subject to extensive first-pass metabolism by the liver [7]. A recent study compared the effects of a COC containing 20 μg EE and 100 μg LNG on the hypothalamic–pituitary–ovarian axis in obese versus nonobese women [27]. PK data for the two contraceptive steroids were also measured. Obese women were found to have significantly larger mean AUC (LNG and EE; $p < 0.05$), longer t½ (LNG; $p < 0.05$) and lower clearance (LNG and EE: $p < 0.05$) compared with normal-weight women. Alterations in volume of distribution were less important contributors, and the authors asserted that alterations in

clearance were the most significant, and most concerning, finding. Obese women also had higher levels of ovarian hormone production (estradiol and progesterone) [27], suggesting greater ovarian activity (and, therefore, potentially decreased contraceptive efficacy) than normal-weight women. The longer t½ identified in obese women corresponded to a longer time for the contraceptive hormones required to reach steady state following a 7-day hormone-free (placebo) interval. In one instance, steady state in one obese participant was not achieved even after the full 21-day pill cycle [27]. This potentially creates a period of time – primarily after pill initiation and possibly during placebo weeks – during which an obese woman using COCs is not adequately protected from pregnancy, or during which any gaps in compliance may significantly increase her risk for contraceptive failure.

Another study compared the PK and pharmacodynamics of a COC containing 30 μg EE and 150 μg LNG in normal-weight and obese women [28]. Obese women were found to have lower AUC, C_{max} and T_{max} (the time to reach C_{max}) as well as an increased t½ of both EE and LNG, compared with normal-weight women. The C_{min} of both hormones were similar across the different BMI categories. Pharmacodynamic assessment consisted of twice-weekly trans-vaginal ultrasounds to measure the presence of ovarian follicles. There was no significant difference in ovarian follicular activity by BMI. The authors concluded that despite the changes in PK parameters seen for LNG and EE, contraceptive efficacy was maintained in the obese participants since their LNG C_{min} did not drop below the level needed to suppress ovulation.

PK studies are rarely powered to evaluate outcomes such as pregnancy. Larger studies that evaluate contraceptive failure rate are few and results are mixed. An analysis of data from the 2002 National Survey of Family Growth found that women with a BMI greater than 30 kg/m^2 had a nonsignificant increased risk of method failure when using COCs for contraception, compared with normal-weight women [29]. A case–control study investigating the pregnancy rate among COC users found a 60% increased risk of unintended pregnancy in all COC users with BMI >27.3 kg/m^2 (odds ratio [OR]: 1.58; 95% CI: 1.11–2.24), and 70% increased risk in users with BMI >32.3 kg/m^2 (OR: 1.72; 95% CI: 1.04–2.82). When only consistent COC users were analyzed, the odds of pregnancy were more than doubled for obese women. The authors state that this translates to an attributable risk of 2–4 additional pregnancies per 100 women-years among overweight and obese COC users [30]. A Cochrane Review of 11 studies that used pregnancy as their primary outcome found that overweight or obese women (BMI >25 kg/m^2) were almost twice as likely to become pregnant while relying on COCs than their normal-weight peers (OR: 1.91; 95% CI: 1.01–3.61) [31]. Data from 50,000 women in the USA, which were collected as part of a prospective, noninterventional cohort study, demonstrated higher oral contraceptive failure rates with higher BMI, when adjusted for age, parity and education level. Women with a BMI of 35 kg/m^2 or greater had a hazard ratio of 1.5 (95% CI: 1.3–1.8) for contraceptive failure, compared with women with a BMI less than 35kg/m ^{2} [32].

By contrast, a secondary analysis of the EURAS-OC study found no difference in overall contraceptive failure rates according to BMI or body weight [33]. When the analysis was stratified by individual progestins, only one – chlormadi-none acetate – was found to be significantly associated with contraceptive failure in obese women. Analysis from the

Contraceptive CHOICE Project found no increase in contraceptive failure rate by BMI category in users of COCs, patch or ring [34]. While the data conflict, the cumulative conclusion seems to be that pregnancy rates among overweight and obese women using COC seem to be similar to or slightly higher than rates among normal-weight women. The large numbers of women included in some studies, and the biological plausibility for altered PK, do suggest the possibility that COC may potentially be less efficacious in obese women.

It has been theorized that extended or continuous use of COC formulations may improve effectiveness compared with traditional monthly cycling in women of normal weight, by reducing or eliminating the hormone-free interval that has been identified as a time period of concern. This has not been conclusively demonstrated. A reanalysis of data from a Phase III clinical trial of the efficacy of a COC containing 20 μg EE and 100 μg LNG found no impact of body weight on pill efficacy. There was no significant difference in pregnancy rates across weight and BMI deciles [35]. However, this may currently be an understudied area of research.

Contraceptive patch

The contraceptive patch contains 6 mg norelgestromin and 0.75 mg EE, and each patch is worn for 7 days [36]. Compared with a daily COC containing the same hormones, the AUC of EE and norelgestromin delivered by the patch are higher than when taken orally [37]. Increased body weight and body surface area were associated with decreases in the AUC of both EE and norelgestromin among patch users, but these were not thought to be clinically significant.

A large randomized trial comparing efficacy of the patch to that of combined oral contraceptives reported two pregnancies in patch users who weighed more than 80 kg [38]. However, women needed to be within 35% of ideal body weight in order to be enrolled, and the actual number of obese or overweight women was not reported. Subsequently, a pooled analysis of data for the contraceptive patch determined that women weighing more than 90 kg had a significantly increased failure rate compared with women weighing less than 90 kg [39]. Of 15 pregnancies that occurred during 22,160 treatment cycles, five of them occurred in women weighing more than 90 kg (who accounted for less than 3% of the study population). The authors concluded that women in this weight category may be at increased risk of contraceptive failure with use of the patch.

Contraceptive vaginal ring

The contraceptive vaginal ring provides a non-oral, nondaily contraceptive method for women interested in short-term birth control. The ring contains a total of 11.7 mg ENG and 2.7 mg EE, and releases these hormones at an average daily rate of 120 μg ENG and 15 μg EE [40]. The ring produces a lower serum peak EE concentration and lower EE AUC (indicating lower total systemic exposure) than either COCs or the patch [38]. In normal-weight women, the peak concentration and AUC of ENG are similar between the ring and COCs.

Efficacy studies of the vaginal ring included very few obese women [41]. A recent study comparing serum and physiologic markers of ovulation in 18 normal-weight and 19 obese

women using the ring found lower EE concentrations in the obese participants, but no difference in ENG concentrations [42]. While this study was too small to assess pregnancy rates, there was no difference in ovarian follicle development or serum progesterone levels between the two groups, suggesting that contraceptive efficacy is maintained in obese women.

Even if combined methods are slightly less efficacious in obese women than in normal-weight women, this is not equivalent to lack of efficacy. The possibility of lower efficacy of some shorter-acting methods should lead to serious consideration of longer-acting methods. However, any method of contraception is more efficacious than no method. If a woman makes an informed choice to use a combined method, she should not be refused contraception based on body weight alone.

Postcoital (emergency) contraception

There are currently two FDA-approved emergency contraceptive pills (ECPs) available in the USA. A levonorgestrel-based regimen involves either a single dose of 1.5 mg LNG or two doses of 0.75 mg LNG taken 12 h apart [43]. In the USA, LNG ECP has been available over the counter for women over the age of 17 years, and this was recently expanded to younger women as well. These dosing regimens are effective at reducing the risk of pregnancy up to 72 h after unprotected intercourse. Ulipristal acetate (UPA), a progesterone agonist/antagonist, is a one-time 30 mg dose that is effective up to 5days after unprotected intercourse [44]. ECPs prevent pregnancy by inhibiting or delaying ovulation, and are most effective when taken soon after unprotected intercourse. When taken within 72 h of unprotected sex, the LNG ECP prevents approximately 50% of pregnancies while UPA prevents up to two-thirds of pregnancies [45].

Only two studies have investigated the effects of obesity on the efficacy of ECPs. Glasier *et al.* performed a meta-analysis of two randomized controlled trials comparing LNG with UPA for emergency contraception [46]. Among several covariates tested, BMI was found to have the greatest impact on risk of pregnancy after using either ECP method, but the risk was greater with LNG than UPA. The risk of pregnancy was four-times greater in obese women who took LNG ECPs compared with normal-weight women (OR: 4.41; $p < 0.05$). Moreau and Trus-sell performed a pooled analysis of UPA efficacy, and found that obese women were twice as likely to experience ECP failure compared with nonobese women (OR: 2.1; 95% CI: 1.0–4.3; $p = 0.04$) [47].

Safety concerns

An overestimation of contraceptive risk in obese women may lead to inadequate provision of effective contraceptive methods. In general, obese women may not receive preventive reproductive health screenings as often as normal-weight women [48]. For all women, including obese women, the risks of pregnancy generally outweigh the risk of potential harm from contraceptives. Hormonal contraception is a safe choice for obese women, in the absence of other contraindicating health conditions. The USA Medical Eligibility Criteria for Contraceptive Use and the WHO Medical Eligibility Criteria for Contraceptive Use are evidence-based resources to guide provision of contraceptives for women with a wide range

of medical conditions [49,50]. Both documents advise that there are no safety concerns with the use of any progestin-only contraceptive methods in obese women. This includes pills, injectables, implants and intrauterine contraception.

Furthermore, combined hormonal contraceptives (CHC) are also considered safe for use. The most concerning potential side effect of CHC is a venous or arterial thrombotic event. Obese women are approximately twice as likely as normal-weight women to experience venous thromboembolism (VTE), and obese women who use COCs are more likely than obese women who do not use COCs to experience VTE [51,52]. However, the absolute risk for VTE in women of reproductive age is small, and there is unlikely to be a significantly higher risk from one type of CHC compared with another [53,54]. Furthermore, risks of VTE in pregnancy and postpartum are substantially higher than risks of VTE during contraceptive use. Thus, CHC are considered appropriate for obese women in the absence of other medical contraindications [45,50]. A summary of recommendations from the CDC and WHO MEC regarding contraceptive use by obese women is presented in Table 3. It should be acknowledged that data to guide contraceptive provision for women with BMI >40 kg/m^2 were limited.

Bariatric surgery

No discussion of contraceptives and obesity would now be complete without consideration of bariatric weight-loss surgery. This has been recognized as one of the most effective – and one of the few proven effective – treatments for obesity. The majority of reproductive-age patients undergoing bariatric surgery are women [55], who are strongly advised to avoid pregnancy for up to 2 years after surgery [56]. The dramatic weight-loss that follows bariatric surgery leads to improvement in hypertension, diabetes and dyslipidemia, and can also lead to resumption of ovulation and normalization of menstrual irregularities [57]. There are very limited data on the use of contraceptives after bariatric surgery, but there are theoretical concerns that both malabsorptive and restrictive procedures could decrease the absorption of oral contraceptives [52,58]. The efficacy of nonoral methods is not believed to be affected by bariatric weight-loss surgery, except that any obesity-related effects that do exist will resolve as excess weight is lost [55].

Concerns for use of oral contraceptives after bariatric surgery are largely related to the type of surgery. There are three main categories of bariatric surgery: restrictive, malabsorptive and combined restrictive–malabsorptive. Purely malabsorptive procedures have fallen out of favor and are rarely performed. Restrictive procedures, which limit the size of the stomach and thus limit the amount of oral intake, include the popular gastric banding operations. Since restrictive procedures do not interfere with the absorptive capacity of the gut, they are not believed to decrease efficacy of oral contraceptives. Restrictive–malabsorptive procedures, however, may be a different story. A common example of such a procedure is the Roux-en-Y gastric bypass. This procedure both surgically limits the size of the stomach (restrictive component) and bypasses a significant portion of the duodenum, intentionally creating a malabsorptive state. This malabsorption may also decrease the ability of the gut to absorb hormones from oral contraceptives, which could in turn decrease their contraceptive efficacy. This concern is based on limited data from poorly designed studies [52]. However,

the concern is sufficient that the US MEC, which otherwise focuses primarily on contraceptive safety, advises against the use of oral contraceptives in women after gastric bypass surgery [45]. For women who have undergone gastric bypass surgery, there is also concern that subsequent malabsorption could reduce the efficacy of ECPs [45]. Table 4 summarizes recommendations for contraceptive use in women who have had bar-iatric weight-loss surgery. Current research in this area is ongoing.

Discussion

To date, providers of hormonal contraceptive methods employ a one-size-fits-all approach. Most PK studies exclude women who are greater than 130% of their ideal body weight and these studies typically note significant interindividual variability in serum concentrations of contraceptive hormones, even among normal-weight participants. Similarly, clinical trials of new contraceptives have historically excluded obese women. However, all women are given the same dosages of contraceptive hormones regardless of weight. The significant variability in serum hormone concentrations among individuals begs the question of whether this one-size-fits-all approach is realistic, especially given the rising prevalence of obesity and the serious consequences of inadequate contraception. The question is also relevant given that the dose of EE in oral contraceptives has steadily decreased over the last several decades. It is unclear whether these lower doses are exposing women to increased risk of contraceptive failure [59].

Evidence to date is reassuring that many contraceptive methods maintain their efficacy in obese women. Despite conflicting information regarding the efficacy of some hormonal contraceptives in obese women, it is important to remember that any contraceptive, even if less efficacious, is a better and safer choice than no method at all. Overweight and obese women are at increased risk of pregnancy complications, including gestational diabetes, hypertensive complications and cesarean delivery [60]. Since it is unclear how much obesity may reduce the efficacy of short-acting contraceptives in particular, it seems overly alarmist to restrict the use of these methods in overweight and obese women. Highly effective, long-acting, reversible contraceptive methods provide the most reliable contraception for all women, regardless of weight. These should be considered first-line methods for obese and overweight women and can be offered to all appropriate candidates.

Conclusion

Obesity affects a continuously growing number of reproductive-aged women, and helping obese women manage their reproductive health is as important as with any chronic disease. Healthcare providers who understand how obesity may affect the efficacy of hormonal contraceptives will be better able to assist their patients in reproductive decision-making. As more obese women chose to undergo bariatric surgery, it will be important to investigate what effects, if any, such surgeries have on contraceptive efficacy. Providing effective contraception is also a crucial part of helping obese women undergo weight loss therapy. Increasing use of long-acting reversible contraception methods has the potential to avoid the PK and pharmacodynamics changes that accompany obesity while maximizing use of the most effective contraceptive methods

Future perspective

Obese women represent a population whose reproductive health is greatly affected by their weight, yet factors that influence contraceptive efficacy in this population are poorly understood. Research is beginning to focus on the best contraceptive methods for overweight and obese women. Elucidating the relationship between obesity and contraceptive efficacy should continue to be a focus of future research, and evaluation of new contraceptive methods should proactively include obese women.

Future directions should also include the integration of contraceptive provision into weight-loss programs. This will enable women to improve their health before undertaking the demands of pregnancy, and will also reduce their risk of obesity-related complications of pregnancy. Encouraging obese women to consider the most effective, reversible contraceptive methods maximizes their contraceptive and noncontraceptive benefits.

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Learning objectives

Upon completion of this activity, participants should be able to:

- Analyze the effects of obesity on pharmacokinetics
- Distinguish contraceptive methods which may be less effective among obese women
- Evaluate the efficacy of emergency contraceptive pills among obese women
- Assess the effects of bariatric surgery on the efficacy of oral contraceptive

Executive summary

Pharmacokinetic implications: cause for concern?

- Obesity is a prevalent health problem and may affect the pharmacokinetics and efficacy of hormonal contraceptives.

Efficacy of hormonal contraceptives among obese women

- Limited data suggest that long-acting reversible contraceptives methods (intrauterine devices and implants) retain excellent contraceptive efficacy in obese women.
- Oral contraceptives, the contraceptive patch and emergency contraceptive pills have been shown to have increased failure rates in obese women compared with normal-weight women. The risk of failure appears to be greatest in those women with the highest BMI (>35 kg/m^2).
- The use of any hormonal contraceptive is more effective at preventing pregnancy than using no method. Obese women should be offered a full range of contraceptive options with a candid discussion of each method's risks, benefits and alternatives.

Table 1

Categories of obesity and weight.

Category	BMI (kg/m^2)
Underweight	<18.5
Normal	18.5–24.9
Overweight	25–29.9
Obese:	≥30
– Class 1	30–34.9
– Class 2	35–39.9
– Class 3	≥40

Data taken from [2].

Table 2

Perfect- and typical-use failure rates for selected methods of hormonal contraception.

Method	Perfect-use failure rate	Typical-use failure rate
Intrauterine contraception levonorgestrel	0.2	0.2
Progestin implants	0.05	0.05
Injectable progestins	0.2	6
Contraceptive pill/patch/ring	0.3	9
Progestin-only pill	0.3	9

Rates refer to the percentage of women using the method who experience an unintended pregnancy during the first year of method use. These apply to the general population; specific estimates are not available for overweight/obese women. Failure rates refer to expected number of pregnancies per 100 woman-years of use.

Adapted with permission from [10].

Table 3

Medical Eligibility Criteria for selected contraceptive methods in obese women.

Contraceptive method	MEC category	Definition
Intrauterine contraception	1	Category 1: no restriction for use of the contraceptive method
Progestin implant	1	Category 1: no restriction for use of the contraceptive method
DMPA	1	Category 1: no restriction for use of the contraceptive method
Progestin only pills	1	Category 1: no restriction for use of the contraceptive method
Emergency contraceptive pills	1	Category 1: no restriction for use of the contraceptive method
Combined pill, patch, ring	2	Category 2: advantages of using the method generally outweigh the theoretical or proven risks

These documents also include categories for relative (category 3: risks generally outweigh advantages) and absolute contraindications (category 4: method should not be used). DMPA: Depot medroxyprogesterone acetate; MEC: Medical Eligibility Criteria.

Data taken from [49,50].

Table 4

Medical Eligibility Criteria for selected contraceptive methods in women who have undergone bariatric weight-loss surgery.

Type	MEC category after restrictive surgery	MEC category after malabsorptive surgery	Definition
Intrauterine contraception	1	1	Category 1: no restriction for use of the contraceptive method
Progestin implant	1	1	Category 1: no restriction for use of the contraceptive method
DMPA	1	1	Category 1: no restriction for use of the contraceptive method
Contraceptive patch/vaginal ring	1	1	Category 1: no restriction for use of the contraceptive method
Combined or progestin-only pill	1	3	Category 3: the theoretical or proven risks usually outweigh the advantages of using the method
Emergency contraceptive pill	1	3	Category 3: the theoretical or proven risks usually outweigh the advantages of using the method

DMPA: Depot medroxyprogesterone acetate; MEC: Medical Eligibility Criteria.

Data taken from [49].