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FAMILY PLANNING (A BURKE, SECTION EDITOR)

Pharmacokinetics of Hormonal Contraception in Individuals with Obesity: a Review

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Abstract

Purpose of Review Obesity continues to affect many women globally. In the USA, almost 40% of all women are obese and many of these women use hormonal contraception for pregnancy prevention. How well hormonal contraceptive works for these individuals has been an area of ongoing research. Pharmacokinetics (PK), the study of drug passage through the body, can shed light on how differences in physiology between obese and non-obese populations can impact drug disposition and subsequent efficacy. This review aims to reflect on these types of studies and empower clinicians with information to help tackle the challenges of the obesity epidemic and help them provide the best contraceptive options to their patients. Here, we present the basics of the mechanisms of action of hormonal contraception, fundamental pharmacokinetic principles, and the latest research into pharmacokinetics, obesity, and hormonal contraception.

Recent Findings New studies focused on the PK of hormonal contraception in women with obesity have shown that while there are distinct differences in how steroid hormones are processed in women with different body mass indices, contraceptive efficacy is likely the same. This is replicated in studies involving a variety of hormonal contraceptive methods.

Summary PK studies allow for a detailed analysis of steroid hormone processing in individuals with obesity. Observing PK parameters at each stage of the passage of these hormones through the body, researchers have drilled down on physiologic differences that accompany obesity. In reviewing these PK parameter differences, however, it appears that while processes are different, the end result of pregnancy prevention is likely not compromised in the setting of obesity. Emergency contraception, which functions by a different mechanism from that of continuous hormonal contraception, is the one area in which obesity has been demonstrated to impact efficacy.

Keywords Pharmacokinetics · Obesity · Hormonal contraception · Birth control · Pharmacodynamics · Efficacy · Effectiveness

Introduction

Obesity remains a massive public health issue in the USA and across the world. According to the Centers for Disease Control, 40% of all women in the USA are obese with a body mass index (BMI) of 30 kg/m^2 or above [1]. Of women aged 20–39 years old, 37% are obese [1] and a majority are using hormonal contraception to prevent pregnancy [2]. Data regarding the impact of obesity on hormonal contraceptive efficacy have been limited as clinical trials have traditionally excluded women who were overweight or obese. Previously, the prevalence of obesity was much lower; thus, including this population with a higher baseline risk of deep venous thrombosis was not as critical as it is now. The Food and Drug Administration has attempted to remedy this issue by recommending that contraceptive clinical trials include participants with obesity [3]. A significant amount of research has been done in recent years focused on this specific issue of hormonal contraception and obesity. Studies, however, have been of varying quality and results have been variable. The question still remains—are standard doses of hormonal contraception effective at preventing pregnancy in women with obesity?

In this article, we will review basic principles related to the mechanism of action of hormonal contraception and provide

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an overview of the differences in pharmacokinetics in women with obese and normal BMIs. We will review the key literature published with a focus on recent trials. With this, we hope to provide healthcare professionals with clarity regarding how hormonal contraceptives are processed in individuals with obesity and how this impacts the efficacy of these methods.

The Mechanism of Action of Hormonal Contraception

Reproductive function is based on cyclic interactions between the hypothalamus, the pituitary, and the ovary. Gonadotropin-releasing hormone (GnRH) is released from the hypothalamus in a pulsatile fashion [4]. GnRH release leads to the release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) from the anterior pituitary. These hormones then trigger the ovary to produce estrogen and progesterone. Depending on the phase of the menstrual cycle, these ovarian hormones fluctuate and provide negative and positive feedback loops to the pituitary and the hypothalamus. This system ultimately results in development of a dominant follicle and ovulation with the release of an egg with the possibility of fertilization and subsequent pregnancy.

Hormonal contraception utilizing a combination of a progestin with or without estrogen works primarily by interrupting or suppressing the feedback loops between the ovary, hypothalamus, and pituitary. When exogenous estrogen (e.g., ethinyl estradiol or EE) and progestin are present, the secretion of FSH and LH is suppressed via a negative feedback loop and this results in ovarian quiescence. In addition, steroid hormones change the consistency of cervical mucus making it less hospitable to sperm and sperm transit and modifying the endometrial lining, further impeding fertilization and implantation.

Pharmacokinetic Principles and Implications for Individuals with Obesity

Pharmacokinetics is the detailed description of the passage and processing of a drug in the body. Four physiologic processes are involved in the pathway through the body: *absorption*, *distribution*, *metabolism*, and *elimination.* Each of these processes can be different in individuals with obesity due to an altered physiology, but it is unclear to what extent these processes might impact hormonal contraception. We review the potential changes for each of these four processes and their impact on key pharmacokinetic parameters here. Some of the most important PK parameters are listed in Table 1.

Absorption

Absorption involves the movement of a drug from the administration site into the circulation. Absorption dictates how quickly (T_{max}) a compound reaches its maximum concentration (C_{max}). Many factors affect drug absorption in individuals with obesity. For example, cardiac output is overall higher in those with obesity [5]. Increased cardiac output can lead to an increased rate and amount of drug that is absorbed as there is more blood flow to the digestive system. People with obesity also have increased gastric emptying rates [6]. With quicker passage of drug through the stomach, the T_{max} can be lower. Some animal models of obesity suggest that transporters and secretion during the absorption process can also be affected by obesity [7], affecting how much drug is bioavailable and therefore the concentration (e.g., C_{max}). Progestins such as levonorgestrel are fully absorbed from the GI tract, while estrogens such as ethinyl estradiol are subject to a first-pass effect where metabolic enzymes in the intestine reduce its bioavailability.

The amount of subcutaneous fat in a person can impact the amount of drug that is absorbed when it is injected subcutaneously or applied transdermally. The rate of blood flow per gram of fat in a person with morbid obesity is markedly different from the rate in a person without obesity [8]. These changes can impact both the rate and extent of drug absorbed via these routes of administration. This again could impact both T_{max} and C_{max}. Studies with contraceptives given by this route have not directly implicated this factor, but it may contribute to the lower exposures seen in women with obesity, which will be described below.

Distribution

Distribution represents the movement of a drug into different compartments of the body. The rate and extent of distribution are determined by body mass, the fat and lean composition of that mass, the blood flow to tissues, and the plasma and tissue binding of the drug. Distribution space is described in terms of the volume of distribution, or *Vd*. The volume of distribution primarily affects the half-life of a drug as indicated by the relationship, $t_{1/2} = 0.693 \times Vd/CL$.

In individuals with obesity, overall lean and fat mass is increased, but the ratio of lean to fat mass is significantly less [9]. A drug with high lipophilicity will have a greater affinity for the larger fat volume in an individual with obesity; therefore, the *Vd* would increase. Multiple different body size markers relevant to obesity are correlated with *Vd*—including lean body weight, fat free mass, and adjusted body weight [10].

The amount of subcutaneous fat in an individual with obesity can also impact drug distribution and the *Vd*. A drug may be intended for the intramuscular space but can be incorrectly

Table 1 Pharmacokinetic parameters, descriptors, and definitions

Parameter	Definition
T_{max}	Time to the maximum measured plasma concentration
C_{max}	Maximum measured plasma concentration over the time span specified
$t_{1/2}$	Final time taken for the plasma concentration to be reduced by half
CL (clearance)	Volume of plasma from which a substance is completely cleared from per unit time
AUC (area under the curve)	The area under the plasma concentration vs. time curve, from time 0 to t

injected into the subcutaneous fat due to the increased depth of the fat. Release from the subcutaneous fat can be slower compared with the intramuscular space; therefore, C_{min} and C_{max} concentrations can be impacted [11].

Plasma protein binding can also be altered in individuals with obesity, subsequently impacting distribution. The primary drug binding protein in plasma is albumin. There does not appear to be a difference in plasma albumin concentration in people with obesity versus those with a normal BMI [12]. However, some lipoproteins that bind albumin are greatly increased in individuals with obesity. This can lead to competitive binding where a drug is displaced from albumin by lipoproteins. Sex hormone binding globulin (SHBG) is an important plasma protein that binds endogenous androgens and estrogens along with progestins. SHBG is decreased in populations with obesity, which can lead to not only increased free circulating steroid hormones, but also decreased overall serum concentrations [13]. The complex roles of albumin and SHBG in the pharmacokinetics of levonorgestrel have been described by Natavio et al. [14] and Reinecke et al. [15].

Metabolism

Metabolism is the enzyme-mediated chemical transformation of a drug. Most drug metabolism occurs in the liver. Enzymes within the liver modify drugs by performing specific chemical reactions, e.g., oxidation, reduction, hydrolysis, conjugation, sulfation, and glucuronidation. Activity of these enzymes is decreased by the presence of pro-inflammatory cytokines; individuals with obesity have increased circulating levels. As a result, altered enzyme function in the livers of individuals with obesity may be partly responsible for some changes in metabolism rates [16]. In addition, fatty liver disease is thought to influence local enzyme function [17], a disease more common in obesity.

Drug transporters play a key role in drug metabolism and elimination. Animal studies suggest that drug transporters are altered in obese populations [18]. Certain hepatic uptake transporters are decreased while efflux transporters are increased.

Elimination

Excretion of drugs and drug metabolites in urine is part of drug elimination. With obesity, many renal parameters are increased: glomerular area, glomerular filtration rates, tubular secretion rates, and renal plasma flow [19]. Multiple studies have confirmed that renal clearance of many drugs is increased in obese individuals [20–22]. BMI also appears to be inversely correlated with urine pH [23]. Reabsorption of a drug is often dependent on the pH of the urine. Both clearance (CL) and reabsorption can impact the half-life ($t_{½}$) of a drug. All contraceptive drugs are moderately to highly lipid soluble and thus undergo extensive tubular reabsorption and have low renal clearances. However, their more water-soluble metabolites are excreted in urine.

Relevant Literature

Prior Studies

Individuals with and without obesity have a number of fundamental physiologic differences. These differences can lead to altered contraceptive steroid hormone levels, but whether this translates to subsequent contraceptive failure remains unclear. Over the last few decades, a number of studies have attempted to answer this question. A portion of these studies have involved larger cohorts focused on assessing the endpoint of pregnancy. Findings from these studies have been mixed and, for non-pill hormonal methods, the number of studies has been limited [24]. These studies also appear to suffer from two main possible confounders: the inability to determine adherence to the contraceptive method and the unknown frequency of intercourse. More recent studies have attempted to control for these elements and suggest that no correlation exists between BMI and hormonal contraceptive effectiveness [25, 26].

Pharmacokinetic (PK) studies can provide insight into how a drug is impacted therapeutically by obesity. However, these studies are not designed to provide definitive proof—e.g., will the contraceptive method fail? Additionally, contraceptive efficacy is not just reliant on the properties of the drug but also

on the fecundity of the individual, intercourse frequency, adherence, and continuation. A summary of the key studies focused on PK, obesity, and hormonal contraception are included in Table 2.

Although the hormonal contraceptives studied here are diverse in terms of composition and route of administration, the trend of the impact on PK parameters is fairly consistent. Plasma concentrations of steroid hormones are generally lower in subjects with obesity.

Recent Studies

In the last 5 years, three additional studies have been published, further confirming these trends. These are summarized in Table 3.

Consistent across all three studies, concentrations of steroid hormones decreased as BMI increased. The Westhoff [39•] study also involved frequent monitoring of ovarian activity and found no evidence of ovulation occurring at different rates in groups of varying BMI. The Luo 2019 study was particularly robust, aggregating data from four different studies, analyzing the PK parameters for 89 subjects using oral contraceptive pills [41••]. The study showed consistent changes in PK parameters for individuals with obesity as found in prior studies. Despite these differences seen in C_{max}, AUC, CL, and $t_{1/2}$, however, these were thought to not have actual clinical impact. Instead, trough levels for both EE and LNG, which were found to be similar between the obese and non-obese groups, suggested that ovulation suppression and pregnancy rates were likely to be similar.

Table 2 Key PK and hormonal contraception in individuals with obesity studies

Study	Hormonal contraceptive	PK findings in subjects with obesity	Additional findings
Oral contraceptive pills (OCPs)			
Doose 2003 [27]	35 mcg EE/1 mg norethisterone	• 32% increase in norethisterone clearance (CL) • Lower plasma concentrations of both	No difference in ovarian suppression or ovulation
Edelman 2009 [28]	20 mcg EE/100 mcg LNG	• EE AUC and C_{max} lower • LNG AUC lower	Trend towards increased HPO axis activity via LH, P and E_2 levels
Westhoff 2010 [29]	30 mcg EE/150 mcg LNG	• EE AUC and C_{max} lower	No significant differences in follicular diameters
Edelman 2013 [30]	20 mcg EE/100 mcg LNG	• Prolonged $t_{1/2}$ for EE and LNG	No association of PK parameters and ovulation suppression
Transdermal patch			
Foegh 2013 [31]	15 mcg EE/75 mcg LNG 25 mcg EE/75 mcg LNG 30 mcg EE/120 mcg LNG	• LNG concentrations 9–30% lower • EE concentrations 14–29% lower	Dose- dependent ovarian suppression
Vaginal ring			
Westhoff 2012 [32]	15 mcg EE/120 mcg etonogestrel (ENG)	• EE concentration lower (15 vs 22 pg/ml) • ENG concentrations similar	Follicular development minimal in both groups
Injectables/implants			
Segall-Gutierrez 2010 [33]	Depo-medroxyprogesterone acetate	• Plasma concentrations 20–30% lower	MPA levels sufficient to prevent ovulation
Sivin 1997 [34]	SC LNG rods (2 rods) 150 mg	• LNG concentration consistently 30–45% lower for women above 70 kg	No pregnancies
Sivin 2001 [35]	SC LNG rods (2 rods) 150 mg (Jadelle)	• Plasma concentrations consistently low in women > 70 kg	LNG concentrations all above 200, minimum needed to prevent pregnancy
Mornar 2012 [36]	Etonogestrel SC implant (Implanon)	• Plasma concentrations 31–54% lower	
Intrauterine systems (IUS)			
Hidalgo 2009 [37]	52 mg LNG IUS	• Lower LNG concentrations after 5 years	
Seeber 2012 [38]	52 mg LNG IUS	• Lower LNG plasma concentrations in BMI > 30 (119 pg/ml) vs BMI < 20 (165 pg/ml)	

Table 3 Recent PK and hormonal contraception in individuals with obesity studies

Study	Hormonal contraceptive	PK findings in subjects with obesity	Additional findings
Transdermal patch			
Westhoff 2014 [39•]	Patch (EE and GSD)	• EE clearance 17% higher • EE exposure 15% lower • EE AUC lowest in highest BMI group • EE C_{max} decreased • GSD AUC decreased • GSD C_{max} decreased • SHBG decreased	Increased rates of follicle like structures in obese women No differences in ovulation events between the groups
IUS			
Creinin 2015 [40]	52 LNG IUS	• LNG concentrations 103 vs 148 pg mL at 36 months (Mirena) • LNG plasma concentration 31% lower (Liletta)	No differences in efficacy between groups
OCP			
Luo 2019 [41••]	Varying doses of EE and LNG	• EE and LNG: o Reduced C_{max}, C_{min}, AUC o $t_{1/2}$ longer o Increased CL o Trough levels similar • No differences in SHBG	

Emergency contraception has been the one area in which the effects of obesity on pharmacokinetics and subsequent efficacy have been clear. One of the most definitive assessments examined the pharmacokinetics of 1.5 mg levonorgestrel (Plan B) in women who were of normal, obese, and extremely obese body weights [14]. As shown in Fig. 1, there were markedly lower C_{max} and AUC values in the latter group. These and related findings have contributed to considerations that obese individuals should receive a double dose of LNG [42•], but several studies are underway investigating if this should be recommended.

A few additional studies have been done in the last five years that explore variations of dosing for women with obesity. Edelman et al. [43] explored two different options for alternative dosing in individuals with obesity. Both continuous cycling and increased doses resulted in similar increases in AUC for both EE and LNG, suggesting that these methods may help remedy the decreases in concentrations seen in women with obesity. Secondary

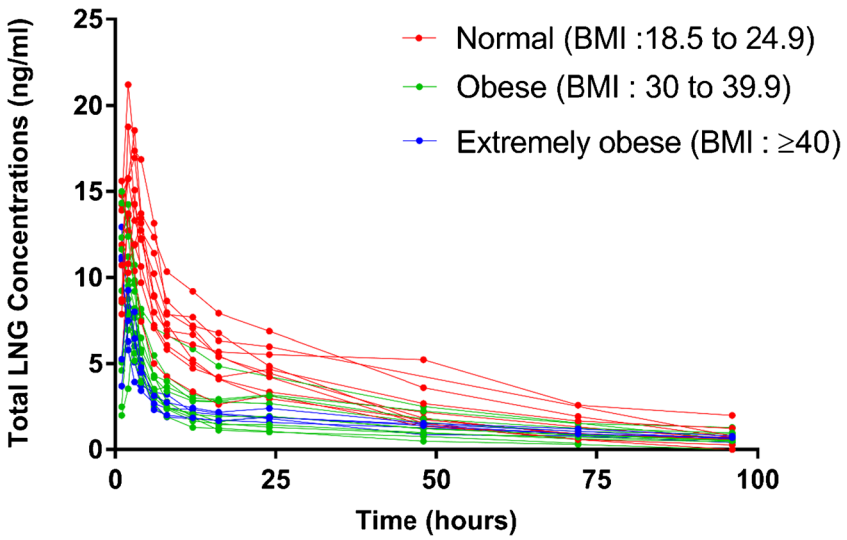

Fig. 1 LNG Concentrations over time by BMI group. Reprinted from [14], with permission from Elsevier

outcomes related to follicle development were also collected and follicular activity was markedly suppressed with both methods when compared with standard low doses and 21/7 cycling for these subjects with obesity.

Safety

The progestin is most relevant to contraceptive efficacy as it is the component responsible for ovulation suppression. Progestin levels have been the focus of most prior research. The estrogen components of these combined methods, however, have benefits of stabilizing the endometrium and reducing breakthrough bleeding. Estrogen also comes with side effects and adverse events. In these studies, the lower estrogen exposure via lower serum concentrations seen in individuals with obesity could lead to increased safety with reduced risks of venous thromboembolism. In addition, side effects of nausea, headache, and breast tenderness may all be decreased due to these lower systemic levels.

Conclusion

Concern regarding the effectiveness of hormonal contraception in individuals with obesity arose in tandem with the obesity epidemic over the last 20 years. As a normal BMI has become a minority state, it is important to ensure that our treatments and drugs work across the full range of BMI. In the last decade, a number of critical studies have been published providing significant insights. We know that obesity impacts the pharmacokinetics of contraceptive steroid hormones. BMI does not appear to be a major risk factor for contraceptive failure except possibly in progestin-based emergency contraception. The exact impact of BMI on contraceptive effectiveness is difficult to determine in shorter acting methods like birth control pills as adherence and compliance are the main drivers of failure.

Overall, the evidence base related to hormonal contraception and obesity suggests that despite significantly altered pharmacokinetics, most hormonal contraception is effective for women with obesity. The use of any contraceptive method, no matter the BMI, prevents more pregnancies than the non-use of contraception.

Compliance with Ethical Standards

Human and Animal Rights and Informed Consent All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

Conflict of Interest Dr. Edelman reports grants from the National Institutes of Health and Merck, along with contract work for Up To Date and HRA Pharma outside the submitted work. Drs. Ramanadhan and Jusko have nothing to disclose.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Prevalence of obesity among adults and youth: United States, 2015–2016. In: Statistics CfDCaPNCfH, editor.: U.S. Department of Health and Human Services; 2017.
2. Kavanaugh ML, Jerman J. Contraceptive method use in the United States: trends and characteristics between 2008, 2012 and 2014. Contraception. 2018;97(1):14–21.
3. Establishing effectiveness and safety for hormonal drug products intended to prevent pregnancy guidance for industry. Office of Medical Products and Tobacco, Center for Drug Evaluation and Research, Food and Drug Administration. 2019.
4. Jensen J, Creinin M. Speroff & Darney's clinical guide to contraception: Wolters Kluwer Health; 2019.
5. Adams JP, Murphy PG. Obesity in anaesthesia and intensive care. Br J Anaesth. 2000;85(1):91–108.
6. Wisen O, Johansson C. Gastrointestinal function in obesity: motility, secretion, and absorption following a liquid test meal. Metabolism. 1992;41(4):390–5.
7. Geier A, Dietrich CG, Grote T, Beuers U, Prüfer T, Fraunberger P, et al. Characterization of organic anion transporter regulation, glutathione metabolism and bile formation in the obese Zucker rat. J Hepatol. 2005;43(6):1021–30.
8. Lesser GT, Deutsch S. Measurement of adipose tissue blood flow and perfusion in man by uptake of 85Kr. J Appl Physiol. 1967;23(5):621–30.
9. Cheymol G. Effects of obesity on pharmacokinetics implications for drug therapy. Clin Pharmacokinet. 2000;39(3):215–31.
10. Green B, Duffull SB. What is the best size descriptor to use for pharmacokinetic studies in the obese? Br J Clin Pharmacol. 2004;58(2):119–33.
11. Nisbet AC. Intramuscular gluteal injections in the increasingly obese population: retrospective study. Bmj. 2006;332(7542):637–8.
12. Edelman AB, Cherala G, Stanczyk FZ. Metabolism and pharmacokinetics of contraceptive steroids in obese women: a review. Contraception. 2010;82(4):314–23.
13. Hautanen A. Synthesis and regulation of sex hormone-binding globulin in obesity. Int J Obes Relat Metab Disord. 2000;24(Suppl 2):S64–70.
14. Natavio M, Stanczyk FZ, Molins EAG, Nelson A, Jusko WJ. Pharmacokinetics of the 1.5 mg levonorgestrel emergency contraceptive in women with normal, obese and extremely obese body mass index. Contraception. 2019;99(5):306–11.
15. Reinecke I, Hofmann B, Mesic E, Drenth HJ, Garmann D. An integrated population pharmacokinetic analysis to characterize levonorgestrel pharmacokinetics after different administration routes. J Clin Pharmacol. 2018;58(12):1639–54.
16. Wisse BE. The inflammatory syndrome: the role of adipose tissue cytokines in metabolic disorders linked to obesity. J Am Soc Nephrol. 2004;15(11):2792–800.

17. Lee YH, Pratley RE. The evolving role of inflammation in obesity and the metabolic syndrome. Curr Diab Rep. 2005;5(1):70–5.
18. Cheng Q, Aleksunes LM, Manautou JE, Cherrington NJ, Scheffer GL, Yamasaki H, et al. Drug-metabolizing enzyme and transporter expression in a mouse model of diabetes and obesity. Mol Pharm. 2008;5(1):77–91.
19. Henegar JR, Bigler SA, Henegar LK, Tyagi SC, Hall JE. Functional and structural changes in the kidney in the early stages of obesity. J Am Soc Nephrol. 2001;12(6):1211–7.
20. Bauer LA, Edwards WA, Dellinger EP, Simonowitz DA. Influence of weight on aminoglycoside pharmacokinetics in normal weight and morbidly obese patients. Eur J Clin Pharmacol. 1983;24(5):643–7.
21. Korsager S. Administration of gentamicin to obese patients. Int J Clin Pharmacol Ther Toxicol. 1980;18(12):549–53.
22. Sketris I, Lesar T, Zaske DE, Cipolle RJ. Effect of obesity on gentamicin pharmacokinetics. J Clin Pharmacol. 1981;21(7):288–93.
23. Li WM, Chou YH, Li CC, Liu CC, Huang SP, Wu WJ, et al. Association of body mass index and urine pH in patients with urolithiasis. Urol Res. 2009;37(4):193–6.
24. Lopez LM, Bernholc A, Chen M, Grey TW, Otterness C, Westhoff C, et al. Hormonal contraceptives for contraception in overweight or obese women. Cochrane Database Syst Rev. 2016;8:CD008452.
25. Holt VL, Scholes D, Wicklund KG, Cushing-Haugen KL, Daling JR. Body mass index, weight, and oral contraceptive failure risk. Obstet Gynecol. 2005;105(1):46–52.
26. Brunnerhuber L, 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(8):637–43.
27. Doose DR, Wang SS, Padmanabhan M, Schwabe S, Jacobs D, Bialer M. Effect of topiramate or carbamazepine on the pharmacokinetics of an oral contraceptive containing norethindrone and ethinyl estradiol in healthy obese and nonobese female subjects. Epilepsia. 2003;44(4):540–9.
28. Edelman AB, Carlson NE, Cherala G, Munar MY, Stouffer RL, Cameron JL, et al. Impact of obesity on oral contraceptive pharmacokinetics and hypothalamic–pituitary–ovarian activity. Contraception. 2009;80(2):119–27.
29. Westhoff CL, Torgal AH, Mayeda ER, Pike MC, Stanczyk FZ. Pharmacokinetics of a combined oral contraceptive in obese and normal-weight women. Contraception. 2010;81(6):474–80.
30. 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(2):220–6.
31. Foegh M, Archer DF, Stanczyk FZ, Rubin A, Mishell DR. Ovarian activity in obese and nonobese women treated with three transdermal contraceptive patches delivering three different doses of ethinyl estradiol and levonorgestrel. Contraception. 2013;87(2):201–11.
32. 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. American Journal of Obstetrics and Gynecology. 2012;207(1):39.e1–.e6.
33. Segall-Gutierrez P, Taylor D, Liu X, Stanzcyk F, Azen S, Mishell DR. Follicular development and ovulation in extremely obese women receiving depo-medroxyprogesterone acetate subcutaneously. Contraception. 2010;81(6):487–95.
34. Sivin I, Lähteenmäki P, Ranta S, Darney P, Klaisle C, Wan L, et al. Levonorgestrel concentrations during use of levonorgestrel rod (LNG ROD) implants. Contraception. 1997;55(2):81–5.
35. Sivin I, Wan L, Ranta S, Alvarez F, Brache V, Mishell DR, et al. Levonorgestrel concentrations during 7 years of continuous use of Jadelle contraceptive implants. Contraception. 2001;64(1):43–9.
36. Mornar S, Chan L-N, Mistretta S, Neustadt A, Martins S, Gilliam M. Pharmacokinetics of the etonogestrel contraceptive implant in obese women. AJOG. 2012;207(2):110.e1–.e6.
37. Hidalgo MM, Hidalgo-Regina C, Bahamondes MV, Monteiro I, Petta CA, Bahamondes L. Serum levonorgestrel levels and endometrial thickness during extended use of the levonorgestrel-releasing intrauterine system. Contraception. 2009. July;80(1):84–9.
38. Seeber B, Ziehr SC, Gschlieβer 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(4):345–9.
39.• Westhoff CL, Reinecke I, Bangerter K, Merz M. Impact of body mass index on suppression of follicular development and ovulation using a transdermal patch containing 0.55-mg ethinyl estradiol/2.1-mg gestodene: a multicenter, open-label, uncontrolled study over three treatment cycles. Contraception. 2014;90(3):272–9 **A study investigating PK parameters for the steroid hormone components of a transdermal contraceptive patch, demonstrating that even in individuals with obesity, ovulation was consistently inhibited with the patch.**
40. Creinin MD, Baker JB, Eisenberg DL, Ginde S, Turok DK, Westhoff CL. Levonorgestrel levels in nonobese and obese women using LNG20, a new intrauterine contraceptive. Obstet Gynecol. 2015;125:84S–5S.
41.•• Luo D, Westhoff CL, Edelman AB, Natavio M, Stanczyk FZ, Jusko WJ. Altered pharmacokinetics of combined oral contraceptives in obesity - multistudy assessment. Contraception. 2019;99(4):256–63 **A study aggregating data from multiple PK studies demonstrating minor changes in PK parameters for the steroid hormones in oral contraceptive pills. Trough levels for hormones were found to be the same in individuals with and without obesity**.
42.• 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(1):52–7 **This study shows that double dosing of LNG emergency contraception in individuals with obesity may remedy the lack of efficacy of single LNG EC doses in this population.**
43. Edelman AB, Cherala G, Munar MY, McInnis M, Stanczyk FZ, Jensen JT. Correcting oral contraceptive pharmacokinetic alterations due to obesity: a randomized controlled trial. Contraception. 2014;90(5):550–6.