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Clarification of contraceptive drug pharmacokinetics in obesity[☆]

William J. Jusko

Department of Pharmaceutical Sciences, University at Buffalo, Buffalo, NY 14214, USA

Abstract

Related to concerns about the role of obesity in the efficacy of contraceptive drugs, a review of the literature was carried out in regard to the pharmacokinetics of ethinyl estradiol and various progestins given by various routes of administration. Most studies show that obese women exhibit modestly lower plasma concentrations of these drugs (circa 30%) when given the same doses as normal-weight women. While the mechanism is uncertain, precedence in the literature suggests that this is due to body weight-related differences in metabolism rates. Confusing in some of the literature is that a few studies have reported erroneously calculated pharmacokinetic parameters after multiple dosing of oral contraceptives. A demonstration of appropriate pharmacokinetic methodology is provided.

Keywords

Contraceptive drugs; Pharmacokinetics; Obesity; Clearance; Volume of distribution; Model-fitting

1. Introduction

There has been concern expressed about the effectiveness of contraceptive drugs in obese women. Over one-third of American women over 20 years old are clinically obese, having a body mass index (BMI) greater than 30 kg/m² [1]. A recent assessment of oral contraceptive (OC) clinical trials by the Food and Drug Administration (FDA) indicated that obesity may increase the risk of unintended pregnancy pointing out that future studies should assess pharmacodynamics (PD) and compliance as contributing factors [2]. Of course, measurement of drug exposure [pharmacokinetics (PK)] will be needed in such studies as well. On the other hand, a survey by McNicholas et al. [3] in 2013 concluded that, “overweight and obese females do not appear to be at increased risk for contraceptive failure when using the contraceptive pill, patch, or vaginal ring.” Owing to these issues and uncertainties, there has been increased attention paid to the PK of contraceptive drugs in obese women. The purposes of this communication are to provide a review of recent PK studies of contraceptive drugs in obesity and to point out some misunderstandings in the interpretation of PK data from some of these studies.

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2. Physiological changes in obesity

Obesity is generally a complicating factor in physiology and in the PK and PD of drugs and hormones. The increase in body weight, besides adding to the mass of excess adipose tissue, produces variable changes in renal, hepatic, endocrine and other organ functions. Reviews including that by Smith [4] point out that, “obesity is associated with multiple endocrine alterations as defined by changes in the level of circulating endogenous hormones and changes in the pattern of secretion or clearance of these circulating molecules.” In particular, there are higher serum estrogen concentrations, lower progesterone concentrations, decreased luteinizing hormone concentrations and altered rhythmic patterns of some of these during the menstrual cycle in obese women [5].

A recent review of the role of obesity in the PK of various drugs has shown that there can be no change, increased and decreased clearances (CL), which along with bioavailability primarily controls overall drug exposures [6]. For example, we found that obesity produces a large decrease in the rate of CYP3A4-mediated metabolism (decreased clearance) of the corticosteroid methylprednisolone [7]. Often there are issues on normalizing PK parameters for ideal or total body weight and, importantly, whether to base drug doses on either ideal or total body weight or some intermediate factor. This review will show that obesity generally results in lower plasma concentration exposures [concentration maximum ($C_{\max}$) and area under the curve (AUC)] of various contraceptive drugs given as standard doses by all common routes of administration.

3. OCs

Obesity tends to be accompanied by moderate reductions in total OC plasma drug concentrations. Doose et al. [8] found a 32% increase in norethisterone apparent clearance (CL/F) and a 47% increase in the CL/F of ethinyl estradiol (EE) in obese women taking oral doses of 1 mg of norethisterone and 35 mcg of EE (Ortho-Novum 1/35TM; Janssen Pharmaceuticals) for 20 days producing lower plasma concentrations of both compounds. Westoff et al. [9] studied the PK of 30 mcg EE and 150 mcg levonorgestrel (LNG) tablets (PortiaTM; Barr Laboratories) after three 21-day cycles in 15 normal-weight and 15 obese women. The key observed exposure parameters from their study are listed in Table 1. The changes in EE AUC and $C_{\max}$ were statistically significant, while those of LNG were not. The authors reported no differences in ovarian suppression or ovulation in the normal-weight and obese women during OC use. The occurrence or tendency for lower (total) EE and LNG concentrations could reflect either or a combination of decreased bioavailability (F) (increased first-pass), increased hepatic metabolism and/or reduced induction of sex hormone-binding globulin (SHBG). Measurement of free or unbound drug in such studies would separate the role of protein binding vs. drug metabolism and help clarify which mechanism may prevail.

Edelman et al. [10] examined the PK of an OC containing 20 mcg EE and 100 mcg LNG (AlesseTM; Wyeth Laboratories) in 10 normal and 10 obese women after 21 days of one dosing cycle (as well as for the first dose in cycle 2). The plasma concentration vs. time profiles for EE at the end of cycle 1 are visibly consistent with those of Westoff et al. [9],

with a lower $C_{\max}$ and smaller AUC over 24 h reflecting lower exposures in obese women. For LNG, the $C_{\max}$ values were similar and the AUC appears lower in obese women. However, there is difficulty in interpreting and comparing the AUC and apparent clearance values in the Edelman study because of the nature of their calculations. These authors obtained plasma concentration measurements at steady-state and extended sampling out to 48 h (C_{48}), but then extrapolated their terminal phase (slope= λ_z) concentrations to infinity (using C_{48}/λ_z). It has long been recognized [11,12] that for linear systems in PK:

$$\text{AUC}_{0-\infty} \text{ Single - Dose} = \text{AUC}_{0-\tau} \text{ Multiple - Dose} \quad (1)$$

where τ is the 24-h dosing interval. For single-doses $\text{CL}/F = \text{Dose}/\text{AUC}_{0-\infty}$, while for multiple doses at steady-state, $\text{CL}/F = \text{Dose}/\text{AUC}_{0-\tau}$. Thus, Edelman's extended AUC is a severe overestimation for comparing multiple-dose exposures with other studies and produces a calculated CL/F that is far too small. This effect can be seen in their article when comparing parameters for their cycle 1 vs. cycle 2 (first-dose) data. Westhoff and Pike [13] correctly pointed out previously that the $\text{AUC}_{0-\tau}$ is the most relevant metric when comparing PK among groups or studies during multiple dosing. While Eq. (1) has been proven mathematically [14], an explanation for its validity is related to the presence of drug remaining from previous doses during the multiple-dose time interval along with the amount of drug absorbed during the measurement day. This accumulation effect can be handled properly for calculation of CL/F by either use of data from only the 0- to 24-h collection interval or by use of the "reverse superposition," method where the time-zero and subsequent underlying extrapolated concentrations are subtracted from the entire last-dose washout curve [14].

Furthermore, Edelman et al. [10] calculated values of apparent volume of distribution using:

$$V_d/F = \text{CL} = \lambda_z \quad (2)$$

where $\lambda_z = 0.693/t_{1/2}$ with the half-life is determined from the terminal phase of drug disposition.

This calculation is also flawed because of their use of an erroneous Dose/AUC for CL . Furthermore, the preferred PK metric is the steady-state volume of distribution (V_{ss} or V_{ss}/F) that reflects total body space as well as equilibrium tissue distribution of drugs. The value of $V_{ss}/\text{Body Weight}$ represents the average tissue/plasma distribution ratio, which would be of special interest in obesity owing to the expanded fat mass and degree of partitioning of the drugs into adipose tissues. Furthermore, Eq. 2 produces an inappropriate estimate of V_{ss} for drugs with relatively rapid clearances [15]. Similar miscalculations of CL and V_d were made in the Edelman et al. studies of only obese women [16, 17] and promulgated in their review article [18].

Appendix A provides a demonstration of the differences in PK parameters for EE and LNG when using both correct and incorrect noncompartmental vs. model-fitting approaches with

multiple-dose data. Model fitting with consideration of the duration of multiple dosing is needed for proper and full elaboration of the PK parameters of an OC.

While the Edelman studies appear to generally confirm the differences in $C_{\max}$ and $AUC_{0-\tau}$ found by Westoff et al. [9], they do have the added merit in capturing the longer terminal half-lives in obese women and showing the slow attainment of steady-state (over about 10 days) in obese women. Their recent PK study [16] followed LNG and EE concentrations out to 168 h after 21 days of dosing of a 20 EE/100 LNG product (Aviane™; Teva) in obese women for a 21-day cycle. The $t_{1/2}$ for LNG was found to be 65 ± 40 h, while that for EE was listed as 467 ± 156 h (viz 19.5 days!). The latter values were derived over a 5-day washout period with very low and irregular EE concentrations and should be further verified. These findings may have implications for the duration of OC effectiveness during intervals between stopping and restarting use of an OC product.

However, the terminal half-life reflects only part of the time-course of drug exposure or AUC. A better metric that accounts for the absorption process and the poly-exponential kinetics of drugs with patterns such as observed for EE and LNG is the “Operational Multiple-Dose Half-Life.” This parameter can be calculated from $t_{1/2op} = \ln 2 \cdot \tau / \ln(C_{\max}/C_{\min})$, where τ is the 24-h dosing interval [19,20]. This value is about 12.5 h for EE and 16.2 h for LNG in normal-weight women and 16.6 h for EE and 21.7 h for LNG for obese women using the mean values from the Westhoff study listed in Table 1 [9]. The $t_{1/2op}$ better accounts for the fluctuations in plasma drug concentrations observed during multiple dosing than does the value calculated from the terminal disposition phase.

There are additional considerations needed when comparing OC PK from different studies. Kuhn et al. [21,22] showed that the PK of EE and LNG can change from single doses to the first cycle to the third multiple-dosing cycle owing to the slow inhibition of hepatic metabolism and slow induction of SHBG by EE. Obesity is accompanied by lower SHBG concentrations (50.4 nmol/L for women with BMI <25 kg/m² and 32.0 nmol/L for BMI ≥ 30 kg/m²) [5] that add a further complication in interpreting these studies. The measurement of free or unbound EE and LNG is needed to better assess whether PK changes are due to either protein binding or to the intrinsic metabolic clearances (or both) of these drugs.

There is an ongoing clinical trial [23] to assess the PK of the 1.5 mg LNG emergency contraceptive pill (Next Choice, Activis; Plan B One-Step™, Teva) in normal, obese and extremely obese women. Part of the premise of these studies is that obese women may have PK consistent with a larger volume of distribution of LNG. It is possible that this expectation was based on flawed PK calculations similar to those described in the Appendix A. On the other hand, Nilsson et al. [24] measured LNG in plasma and fat after 7 days of oral dosing with 250 mcg LNG and 2 mg of estradiol valerate (Cyclabil™; Lieras). At 12 h after the last dose, plasma LNG concentrations averaged 559 ± 209 pg/mL, while fat tissue concentrations averaged 4410 ± 1060 pg/mL, a tissue:plasma ratio of 7.9. Thus, some expansion of the V_{ss} of LNG along with prolongation of the $t_{1/2}$ is expected in obesity. Adipose tissue also appears capable of a small degree of biotransformation of various drugs that could account for increased contraceptive drug clearances. Ellero et al. [25] found very low levels of the mRNA for 20 xenobiotic-metabolizing CYP genes in subcutaneous and

visceral white adipose tissue of women. It is thus of great interest that Edelman et al. [26] examined the plasma concentrations of LNG during the first 2.5 h after giving 1.5 mg doses of LNG (Next Choice™; Activis) to 5 obese (BMI ≥ 30 kg/m²) and 5 normal-weight women. They had also measured unbound LNG and SHBG concentrations. The $C_{\max}$ of total LNG was 5570 and 10,300 pg/mL, while the free concentrations were 65 and 89 pg/mL in the obese and normal-weight women receiving the same dose. Only the differences in total LNG were statistically significant implicating differences due to SHBG binding rather than metabolism rates. Further studies with more women should be performed where the full time-course of total and free plasma drug concentrations is measured in order to calculate all relevant PK parameters and, in particular, assessment of PD is needed.

4. Other routes of contraceptive drug dosing

Segall-Gutierrez et al. [27] injected 104 mg doses of depo-medroxyprogesterone acetate (Depo-Provera™; Pfizer) subcutaneously (SC) in 5 normal-weight (BMI <25 kg/m²), 5 moderately obese (BMI 30–39.9 kg/m²) and 5 very obese (BMI 41–55 kg/m²) women. Plasma concentrations of the drug at 4, 8, 12 and 14 weeks after dosing were 20% to 30% lower in the obese women. However, the concentrations of MPA were stated to remain above the level needed to prevent ovulation in the obese women.

The subcutaneous product Norplant™ (Wyeth Laboratories) consists of six Silastic™ (Dow Corning) rods, each containing 36 mg of LNG, that release LNG over several years producing a steady input rate of 60 to 80 mcg/day initially that later diminishes to about 30 mcg/day. This produced early plasma LNG concentrations averaging about 450 pg/mL that decline to about 250 pg/mL over 4 years [28]. Plasma LNG concentrations after Norplant were appreciably and significantly lower in women with higher body weights. Sivin et al. [29] examined LNG concentrations in women using an SC LNG ROD product (Lieras) consisting of two 43-mm rods, each containing 75 mg of LNG. They showed that LNG concentrations over a 3-year period were consistently 30% to 45% lower in women weighing over 70 kg compared to women weighing less. Sivin et al. [30] performed similar studies with the Jadelle™ (Bayer Healthcare) implant that consists of two flexible cylindrical implants each containing 75 mg of LNG. They found plasma concentrations of LNG over several years that were consistently lowest in women weighing over 70 kg. In general, PK clearances are typically proportional to $BW^{0.67}$ (BW=body weight) or to body surface area for most drugs, and thus, lower plasma concentrations are expected when the same doses are given to heavier women [31]. Sivin et al. [30] noted that there was a strong correlation between the body weights of the women and the Ponderal Index, a measure similar to the BMI. All of their weight groups appeared to maintain LNG concentrations above 200 pg/mL, which was stated as the minimum needed to protect against pregnancy for the SC LNG products studied.

The etonorgestrel SC implant (Implanon™; Organon) is a rod containing 68 mg of drug with an initial release rate of 60–70 mcg/day. Mornar et al. [32] compared etonorgestrel plasma concentrations in 4 normal and 13 obese women with frequent sampling over the first 300 h and then at 3 and 6 months. The obese women exhibited plasma concentrations of etonorgestrel that were generally 31% to 54% lower than normal-weight women.

Foegh et al. [33] measured plasma concentrations of EE and LNG in about 25 nonobese and 15 obese women who received one of three experimental (Corium International) transdermal patches designed to provide daily releases of 75 mcg LNG/15 mcg EE, 100 mcg LNG/25 mcg EE and 120 mcg LNG/30 mcg EE and who were followed for three 28-day cycles. In general, LNG concentrations were 9% to 30% lower and EE concentrations were 14 to 29% lower in the obese women. The authors cite literature studies indicating that for another transdermal patch, Ortho Evra™ (Janssen), which releases 150 mcg/day of norelgestromin and 35 mcg/day of EE, women weighing over 90 kg may have significantly increased pregnancy rates. This admonition is also stated in the Ortho Evra product label.

Mirena™ (Bayer Healthcare) is an intrauterine system (IUS) that contains 52 mg of LNG in a cylindrical reservoir releasing the drug (initially 20 mcg/day) into the uterus for the FDA-approved placement duration of 5 years. Lower LNG concentrations are found in obese women using Mirena. Seeber et al. [34] observed LNG plasma concentrations averaging 191 (37 CV%) at 12 months, 157 (43%) at 24 months, 134 (31%) at 36 months and 133 (29%) pg/mL at 60 months. The mean LNG concentrations were lower in women with greater BMI: 165 (35%) when BMI <20 kg/m² and 119 (36%) pg/mL when BMI ≥ 30 kg/m². Hidalgo et al. [35] also found lower LNG concentrations in obese women using Mirena after 5 years. Medicines360 [36] reported about 25% lower LNG concentrations in obese women at various times over 36 months during use of Liletta™ (Activis Pharma and Medicines360), a similar IUS containing 52 mg LNG and releasing 18.6 mcg/day initially. However, their product literature indicates that there was no apparent effect of BMI or body weight on contraceptive efficacy. A study by Creinin et al. [37] with Mirena reported average LNG concentrations of 148.5 pg/mL in normal-weight women and 103.2 pg/mL in obese women at 36 months. They showed a similar 31% difference in LNG plasma concentrations for Liletta.

Contraceptive vaginal rings (Nuvaring™; Merck) that release 15 mcg/day EE and 120 mcg/day etonorgestrel were assessed by Westhoff et al. [38] in 20 normal-weight and 20 obese (BMI ≥ 30 kg/m²) women. The mean plasma concentrations of EE were 15.0 in obese vs. 22.0 pg/mL in the normal women over a 21-day period. The plasma concentrations of etonorgestrel were similar, 1138 vs. 1258 pg/mL, in the corresponding groups.

For both the intrauterine and vaginal routes of contraceptive drug administration, all or part of the efficacy of the drugs is premised on the local delivery and actions in the uterus, with the peripheral plasma concentrations being of secondary concern. The mechanism(s) for the generally lower drug concentrations found in obese women after all of these nonoral routes of administration remains unclear. There exists the possibility of reduced release and/or absorption from these dosage forms and well as more rapid hepatic (and perhaps adipose) metabolism. However, LNG has good solubility and permeability and altered absorption seems unlikely. None of these studies included measurement of unbound drug and thus any complications from differences and changes in SHBG binding cannot be discerned. Concerns for changes in volume of distribution owing to an expanded fat mass are unlikely to affect either the AUC or the steady-state plasma concentrations (C_{ss}) as these latter PK metrics are controlled by the input rate ($F \cdot \text{Dose} / \tau$) and clearance of the drug (viz. $C_{ss} = F \cdot \text{Dose} / (CL \cdot \tau)$).

5. Role of protein binding

The binding of LNG to SHBG and the changes that occur in various circumstances complicate the interpretation of progestin and EE concentrations in plasma. As with several other hormones and fat-soluble vitamins, there is binding to specific circulating globulin proteins in plasma. This provides an added central plasma pool of the drug or hormone and serves to alter access to various tissues. The “Free Hormone Hypothesis” argues that binding of sex steroids to strongly binding proteins such as SHBG reduces the availability of free drug to diffuse into many body tissues [39]. Thus, SHBG binding of LNG and EE may have a protective role for some tissues. A recent publication in this journal [40] has largely endorsed the free drug hypothesis in arguing for the relevance of measurements of unbound LNG concentrations in obese women [26]. However, as reviewed by Smith et al. [41], there are many exceptions to the application of the free hormone hypothesis. Sites such as the endometrium with progestin receptors that bind the drug more strongly than do SHBG or albumin may readily take up the drug or hormone. Other in vitro research has indicated that binding to SHBG appears to augment the availability and actions of sex hormones with their target tissues as their cell membranes have receptors that interact with the SHBG– hormone complex to trigger signaling mechanisms within the cell [42,43]. Also, there is indication that megalin, an endocytic receptor in reproductive tissues, acts as a pathway for cellular uptake of biologically active sex hormones bound to SHBG [44,45]. Thus, it is difficult to interpret the occurrence of more or less free drug or hormone and changes in SHBG in plasma without a more thorough understanding of the dynamics of target tissues and the endocrine system. More insightful and comprehensive studies of the PD of contraceptive drugs are needed in comparing normal and obese women to help interpret the changes observed in SHBG, protein binding and PK.

6. General perspectives

Considerable attention has been paid to assessing the PK of contraceptive drugs in obese women in view of the uncertainty that exists regarding their efficacy and safety [2,3]. When identical doses or release rates of these agents are given to normal and obese women, nearly all studies with EE and various progestins in various types of dosage forms and routes of administration have shown lower exposures in overweight women. The differences in exposure metrics are typically modest. Although concern for alterations in exposure for any drug must be assessed in view of the therapeutic index, the FDA usually considers drug interaction alterations of 1.25- to 2-fold to be “weak,” 2- to 5-fold to be “moderate,” and greater than 5-fold to be “strong” [46]. It is difficult to believe that possible differences in contraceptive efficacy in obese women can be attributed to the modest degree of altered PK alone. Very simply, clearances increase and exposures decrease in some proportion to body size [6,31]. Furthermore, if drug exposure on its own contributes to any adverse effects, obese women may have some degree of “protection” with their lower observed drug concentrations. There is likely a constellation of pathophysiological and PD factors besides SHBG and drug exposures, as well as compliance [2], that need careful evaluation in assessing contraceptive drug effects in obese women.

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Appendix A

The purpose of this section is to compare PK parameters obtained for typical multiple-dose data for LNG and EE using “noncompartmental” (NCA) and model-fitting approaches. Fig. 1 shows some representative [47] time-courses of mean plasma concentrations of LNG and EE over 24 h obtained after 21 days of multiple dosing of an OC containing 150 mcg LNG and 30 mcg EE (similar to the data in Ref. [9]). With such duration of dosing and the occurrence of essentially identical 0- and 24-h plasma concentrations, steady-state is highly probable. Thus, the conditions for application of Eq. (1) are relevant. The Phoenix WinNonlin software (Certara) was used to calculate the AUC values and other PK parameters from these data. (It can be noted that the Phoenix software instructions explain how to properly use AUC values to calculate clearance).

Table A1 lists the NCA PK parameters obtained for LNG and EE from Fig. 1. It can be seen that the $AUC_{0-\infty}$ is far larger than the $AUC_{0-\tau}$. The true apparent clearance (CL/F) is 1.37 L/h for LNG, while that obtained improperly using the full AUC is much smaller, 0.44 L/h. The values of V_d/F obtained using Eq. (2) is 91.2 L with the correct CL/F and was 29.4 L with the incorrect Dose/AUC. Differences in the same directions are seen for EE. These are the types of misuse of the Phoenix NCA software made by Edelman et al. [10,16–18].

Table A2 provides PK parameters obtained for LNG and EE by model fitting of the data based on first-order absorption (k_a), two-compartmental distribution and clearance, and accounting for 21-day multiple dosing. The Adapt 5 program [48] was used in order to control for possible differences in the software. It can be seen that the apparent CL/F is identical to that from the NCA based on 0–24 h data for both compounds. However, the model-determined V_{ss}/F values are smaller than the NCA-derived V_d/F . Thus, the latter does not reflect the true distribution kinetics of the drug. The difference is greater for EE, a compound cleared much faster than LNG. This is expected as it has been long appreciated that Eq. (2) only approximates the true V_{ss} with greater divergence from the true value found for more rapidly eliminated drugs [15]. Lastly, it can be noted that when drugs are given orally with uncertain bioavailability (F), it is appropriate to qualify the parameters by listing them as “apparent” with symbols such as CL/F and V_d/F .

Table A1

Comparison of noncompartmental PK parameters for LNG and EE using multiple-dose plasma concentration vs. time data

Parameter (units)	Definition	LNG	EE
λ_z (h^{-1})	Terminal slope	0.015	0.045
$t_{1/2}\lambda_z$ (h)	Terminal half-life	46.2	15.4
AUC_{0-24} (pg.h/mL)	Area, 0 to 24 h	109,602	1040

Parameter (units)	Definition	LNG	EE
$AUC_{0-\infty}$ (pg.h/mL)	Area, 0 to time ∞	338,148	1468
CL/F (L/h)	Apparent clearance	1.37	28.85
V_d/F (L)	Apparent volume	91.2	641
Dose/ $AUC_{0-\infty}$ (L/h)	“Wrong clearance”	0.44	20.42
V_d (L)	“Wrong volume”	29.4	454

Table A2

Comparison of two-compartment model-fitted PK parameters for LNG and EE using multiple-dose plasma concentration vs. time data

Parameter (units)	Definition	LNG	EE
k_a (h^{-1})	Absorption rate constant	0.842	0.332
V_C/F (L)	Central volume	13.6	43.5
V_T/F (L)	Peripheral volume	65.6	450.3
V_{ss}/F (L)	Total volume ($V_C + V_T$)	79.2	493.8
CL_D/F (L/h)	Distribution clearance	8.54	51.6
CL/F (L/h)	Apparent clearance	1.37	28.85

References

- Centers for Disease Control and Prevention. <http://www.cdc.gov/nchs/hus/contents2013>
- Yamazaki M, Dwyer K, Sobhan M, Davis D, Kim M-J, Soule L, et al. Effect of obesity on the effectiveness of hormonal contraceptives: an individual participant data meta-analysis. *Contraception*. 2015; 92:445–52. [PubMed: 26247330]
- McNicholas C, Zhao Q, Secura G, Allsworth JE, Madden T, Peipert JF. Contraceptive failures in overweight and obese combined hormonal contraceptive users. *Obstet Gynecol*. 2013; 121:585–92. [PubMed: 23635622]
- Smith SR. The endocrinology of obesity. *Endocrinol Metab Clin*. 1996; 25:921–42.
- Yeung EH, Zhang C, Albert PS, Mumford SL, Ye A, Perkins NJ, et al. Adiposity and sex hormones across the menstrual cycle: the BioCycle study. *Int J Obes*. 2013; 37:237–43.
- Hanley MJ, Abernethy DR, Greenblatt DJ. Effect of obesity on the pharmacokinetics of drugs in humans. *Clin Pharmacokinet*. 2010; 49:71–87. [PubMed: 20067334]
- Dunn TE, Ludwig EA, Slaughter RL, Camara DS, Jusko WJ. Pharmacokinetics and pharmacodynamics of methylprednisolone in obesity. *Clin Pharmacol Ther*. 1991; 50:536–49.
- 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; 44:540–9. [PubMed: 12681003]
- Westoff CL, Torgal AH, Mayeda ER, Pike MC, Stanczyk FZ. Pharmacokinetics of a combined oral contraceptive in obese and normal weight women. *Contraception*. 2010; 81:474–80. [PubMed: 20472113]
- Edelman AB, Carlson NE, Cherala G, Munar MR, Stouffer RL, Cameron JL, et al. Impact of obesity on oral contraceptive pharmacokinetics and hypothalamic–pituitary–ovarian activity. *Contraception*. 2009; 80:119–27. [PubMed: 19631786]
- Wagner JG, Northam JHL, Always CD, Carpenter OS. Blood levels of drug at the equilibrium state after multiple dosing. *Nature*. 1965; 207:1301–2. [PubMed: 5884654]

12. Kanarkowski R, Tornatore KM, D'Ambrosio R, Gardner MJ, Jusko WJ. Pharmacokinetics of single and multiple doses of ethinylestradiol and levonorgestrel in relation to smoking. *Clin Pharmacol Ther.* 1988; 43:23–31. [PubMed: 3121231]
13. Westhoff C, Pike M. Pharmacokinetics of a combined oral contraceptive in obese and three normal-weight women. *Contraception.* 2010; 82:581–2. [PubMed: 21074026]
14. Bauer LA, Gibaldi M. Computation of model-independent pharmaco-kinetic parameters during multiple dosing. *J Pharm Sci.* 1983; 72:978–9. [PubMed: 6620166]
15. Jusko WJ, Gibaldi M. Effects of change in elimination on various parameters of the two-compartment open model. *J Pharm Sci.* 1972; 61:1270–3. [PubMed: 5050376]
16. Edelman AB, Cherala G, Munar MY, DuBois B, McInnis M, Stanczyk FZ, et al. Prolonged monitoring of ethinyl estradiol and levonorgestrel levels confirms and altered pharmacokinetic profile in obese oral contraceptive users. *Contraception.* 2013; 87:220–6. [PubMed: 23153898]
17. 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; 90:550–6. [PubMed: 25070547]
18. Edelman AB, Cherala G, Stanczyk FZ. Metabolism and pharmacokinetics of contraceptive steroids in obese women: a review. *Contraception.* 2010; 82:314–23. [PubMed: 20851224]
19. Dutta S, Reed RC. Functional half-life is a meaningful descriptor of steady-state pharmacokinetics of an extended-release formulation of a rapidly cleared drug: as shown by once-daily divalproex-ER. *Clin Drug Investig.* 2006; 26:681–90.
20. Sahin S, Benet LZ. The operational multiple dosing half-life: a key to defining drug accumulation in patients and to designing extended release dosage forms. *Pharm Res.* 2008; 25:2869–77. [PubMed: 19015955]
21. Kuhn W, Al-Yacoub G, Fuhrmeister A. Pharmacokinetics of levonorgestrel and ethinylestradiol in 9 women who received a low-dose oral contraceptive over a treatment period of 3 months and, after a wash-out phase, a single oral administration of the same contraceptive. *Contraception.* 1992; 46:455–69. [PubMed: 1458892]
22. Kuhn W, Staks T, Jutting G. Pharmacokinetics of levonorgestrel and ethinylestradiol in 14 women during three months of treatment with a tri-step combination oral contraceptive: serum protein binding of levonorgestrel and influence of treatment on free and total testosterone levels in the serum. *Contraception.* 1994; 50:563–79. [PubMed: 7705098]
23. Natavio M. Effects of obesity on pharmacokinetics of the levonorgestrel emergency contraceptive pill. *ClinicalTrials.gov*, NCT02104609. 2015
24. Nilsson CG, Haukkamaa M, Vierola H, Luukkainen T. Tissue concentrations of levonorgestrel in women using a levonorgestrel-releasing IUD. *Clin Endocrinol (Oxf).* 1982; 17:529–36. [PubMed: 6819901]
25. Ellero S, Chakhtoura G, Barreau C, Langouet, Benelli C, Penicaud L, et al. Xenobiotic-metabolizing cytochromes P450 in human white adipose tissue: expression and induction. *Drug Metab Dispos.* 2010; 38:679–86. [PubMed: 20035023]
26. Edelman AB, Cherala G, Blue SW, Erikson DW, Jensen JT. Impact of obesity on the pharmacokinetics of levonorgestrel-based emergency contraception: single and double dosing. *Contraception.* 2016; 94:52–7. [PubMed: 27000996]
27. Segall-Gutierrez P, Taylor D, Liu X, Stanczyk FZ, Azen, Mishell DR. Follicular development and ovulation in extremely obese women receiving depo-medroxyprogesterone acetate subcutaneously. *Contraception.* 2010; 81:487–95. [PubMed: 20472115]
28. Olsson S-E, Odland V, Johansson EDB, Nordstrom M-L. Plasma levels of levonorgestrel and free levonorgestrel index in women using Norplant implants or two covered rods (Norplant-2). *Contraception.* 1987; 35:215–28. [PubMed: 3111784]
29. Sivin I, Lahteenmaki P, Ranta S, Darney P, Klaisle C, Wan L, et al. Levonorgestrel concentrations during use of levonorgestrel rod (LNG ROD) implants. *Contraception.* 1997; 55:81–5. [PubMed: 9071516]
30. 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; 64:43–9. [PubMed: 11535213]

31. McLeay SC, Morrish GA, Kirkpatrick CMJ, Green B. The relationship between drug clearance and body size. *Clin Pharmacokinet.* 2012; 51:319–30. [PubMed: 22439649]
32. Mornar S, Chan L-N, Mistretta S, Neustadt A, Martins S, Gilliam M. Pharmacokinetics of the etonogestrel contraceptive implant in obese women. *Obstet Gynecol.* 2012; 207:110.e1–6.
33. 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; 87:201–11. [PubMed: 23036478]
34. Seeber B, Ziehr SC, Gschliesser A, Moser C, Mattle V, Seger, et al. Quantitative levonorgestrel plasma level measurements in patients with regular and prolonged use of the levonorgestrel-releasing intrauterine system. *Contraception.* 2012; 86:345–9. [PubMed: 22402256]
35. Hidalgo MM, Hidalgo-Regina C, Bahamondes V, Monteiro I, Petta CA, Bahamondes L. Serum levonorgestrel levels and endometrial thickness during extended use of the levonorgestrel-releasing intrauterine system. *Contraception.* 2009; 80:84–9. [PubMed: 19501221]
36. Food & Drug Administration. Clinical Pharmacology Review. Liletta; 2014.
37. 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; (Suppl 1):845–55. [PubMed: 26348185]
38. 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. *Obstet Gynecol.* 2012; 207:e1–39.
39. Mendel CM. The free hormone hypothesis: a physiologically based mathematical model. *Endocr Rev.* 1989; 16:232–74.
40. Cherala G, Edelman A, Dorflinger L, Stanczyk FZ. The elusive minimum threshold concentration for contraceptive efficacy. *Contraception.* 2016; 94:104–8. [PubMed: 27000997]
41. Smith DA, Di L, Kerns EH. The effect of plasma protein binding on in vivo efficacy: misconceptions in drug discovery. *Nat Rev Drug Discov.* 2010; 9(12):929–39. [PubMed: 21119731]
42. Rosner W, Hyb DJ, Khan SM, Nakhla AM, Romas NA. Sex hormone-binding globulin mediates steroid hormone signal transduction at the plasma membrane. *J Steroid Biochem Mol Biol.* 1999; 69:481–5. [PubMed: 10419028]
43. Rosner W, Hryb DJ, Kahn SM, Nakhla AM, Romas NA. Interactions of sex hormone binding globulin with target cells. *Mol Cell Endocrinol.* 2010; 316:79–85. 2010. [PubMed: 19698759]
44. Hammes A, Andreasson TK, Spoelgen R, Ralla J, Hubner N, Schulz H, et al. Role of endocytosis in cellular uptake of sex steroids. *Cell.* 2005; 122:751–62. [PubMed: 16143106]
45. Willnow TE, Nykjaer A. Cellular uptake of steroid carrier proteins — mechanisms and implications. *Mol Cell Endocrinol.* 2010; 316:93–102. [PubMed: 19646505]
46. Food and Drug Administration. Guidance for industry. Drug interaction studies — study design, data analysis, implications for dosing, and labeling recommendations. 2012 in press.
47. Jusko WJ. Perspectives on variability in pharmacokinetics of an oral contraceptive product. *Contraception.* 2017; 95:5–9. [PubMed: 27475034]
48. D'Argenio, DZ., Schumitzky, A., Wang, X. ADAPT 5 user's guide: pharmacokinetic/pharmacodynamic systems analysis software. Los Angeles: Biomedical Simulations Resource; 2009.

Fig. 1.

Typical time-courses of LNG and EE plasma concentrations after 21 days dosing of 150 mcg LNG and 30 mcg EE in normal-weight healthy women [47].

Table 1
Comparison of EE and LNG PK in normal and obese women [geometric mean ($\pm$ SD)]

EE	Normal	Obese	LNG	Normal	Obese
AUC (pg·h/mL)	1414 (1043/1917)	1077 (750/1548)	AUC (ng·h/mL)	86 (62/119)	80 (45/142)
C _{max} (pg/mL)	130 (94/178)	86 (58/127)	C _{max} (ng/mL)	7.0 (5.2/9.4)	5.6 (3.9/8.1)
C _{min} (pg/mL)	34.2 (23.6/49.6)	31.5 (21.4/46.5)	C _{min} (ng/mL)	2.5 (1.5/4.0)	2.6 (1.5/4.5)
t _{1/2} (h)	28 (15/53)	30 (20/45)	t _{1/2} (h)	38 (19/75)	74 (40/137)