Original article

Pharmacokinetics of the 1.5 mg levonorgestrel emergency contraceptive in women with normal, obese and extremely obese body mass index ☆,☆☆

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ABSTRACT

Objective: To assess the pharmacokinetics (PK) of levonorgestrel after 1.5 mg oral doses (LNG-EC) in women with normal, obese and extremely obese body mass index (BMI).
Study design: The 1.5 mg LNG dose was given to healthy, reproductive-age, ovulatory women with normal BMI (mean 22.0), obese (mean 34.4), and extremely obese (mean 46.6 kg/m^2) BMI. Total serum LNG was measured over 0 to 96 h by radioimmunoassay while free and bioavailable LNG were calculated. The maximum concentration ($Cmax$), time to maximum concentration ($Tmax$), and area under the curve (AUC) of LNG were assessed. Pharmacokinetic parameters calculated included half-life ($t1/2$), clearance (CL) and volume of distribution (Vss).
Results: Ten normal-BMI, 11 obese-BMI, 5 extremely obese-BMI women were studied. After LNG-EC, mean total LNG *metrics* were lower in the obese and extremely obese groups compared to normal ($Cmax$ 10.5 and 10.5 versus 16.2 ng/mL, both p<.01; AUC 208 and 197 versus 360 h × ng/mL, both p<.05). Mean bioavailable LNG $Cmax$ was lower in obese (7.03 ng/mL, p<.05) and extremely obese (7.53 ng/ml, p=.198) compared to normal BMI (9.39 ng/mL). Mean bioavailable LNG AUC values were lower in obese and extremely obese compared to normal (131.6 and 127.5 vs 185.0 h × ng/mL, p<.05 for both).
Conclusions: Obese and extremely obese women were exposed to lower total and bioavailable LNG than normal BMI women.
Implications: Lower 'bioavailable' (free plus albumin bound) LNG AUC in obese women may play a role in the purported reduced efficacy of LNG-EC in obese users.

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1. Introduction

Obesity has been identified as a risk factor for emergency contraceptive (EC) failure. Pooled analyses of prior randomized controlled studies

designed to assess levonorgestrel (LNG) efficacy have shown a decrease in efficacy of LNG-EC with increasing body weight and body mass index (BMI) [1–3]. Gemzell-Danielsson contended that there was no evidence to support the hypothesis of loss of EC efficacy in subjects with high BMI or bodyweights [4].

Two studies have examined the pharmacokinetics of 1.5 mg doses of LNG in relation to obesity. Praditpan et al. assessed the PK of 1.5 mg doses of LNG in 16 normal and 16 obese women and found that the $Cmax$ and AUC of LNG were nearly half the normal values in the obese women [5]. Calculated values of free LNG were also lower. Edelman et al. found similar differences for $Cmax$ in obesity, but a curtailed PK sampling over 2.5 h was performed and thus other PK parameters could not be calculated [6]. While the FDA has numerous Guidances that provide advice on performing PK and PD studies in subjects with altered physiology, there is no Guidance for obesity and thus no indication of what changes in PK and efficacy would be clinically important.

We assessed the pharmacokinetics of levonorgestrel (LNG) after 1.5 mg oral doses in women with normal, obese and extremely obese

BMI using comprehensive pharmacometric methodology. The primary objective was to compare various exposure metrics and PK parameters of LNG in relation to BMI. Our hypothesis is obese BMI users of LNG-EC have PK profiles that are consistent with reduced plasma protein binding of LNG and that these alterations affect the primary mechanism of action of LNG-EC, which is inhibition of ovulation.

2. Methods

2.1. Study subjects

A prospective cohort study was conducted at the University of Southern California (USC) in Los Angeles, CA, from March 2013 to May 2016 after IRB approval with listing in ClinicalTrials.gov (NCT02104609). We enrolled English- and Spanish-speaking women aged 18–35 years with regular menstrual cycles (24–35 days) and with either normal (BMI 18.5–24.9 kg/m^2), obese (BMI=30–39.9 kg/m^2), or extremely obese (BMI≥40 kg/m^2) BMIs. Women were excluded if they were seeking pregnancy, using hormonal contraception, smokers, taking medication that might interact with LNG-EC (http://drug-interactions.medicine.iu.edu), or had pre-existing renal or liver disease and thyroid, pituitary, adrenal or ovarian disorders.

We scheduled a screening visit during the mid-luteal phase of the menstrual cycle, and obtained informed consent. Subject height, weight, and hip circumference were measured while wearing nonrestrictive undergarments, and calculated BMI. The scale was regularly maintained by our hospital's biomedical engineering department. A comprehensive metabolic panel (CMP) and mid-luteal progesterone (P4) serum sample were obtained. The participant was enrolled into the study if the CMP did not indicate evidence of renal or liver disease and if the mid-luteal P4 was>3 ng/ml, an indication of presumptive ovulation.

On day 8 (+/− 1 d) of the menstrual cycle, participants presented to the USC Clinical Trials Unit after an overnight fast for venous catheter placement. A single dose of levonorgestrel 1.5 mg (Plan B One Step™, Teva, North Wales; Next Choice One Dose™, Activis Pharma, Parsippany, NJ, USA) was given with 200 mL water at time 0, before venous sampling. Blood samples were drawn at 0, 1, 2, 3, 4, 6, 8, 12, 16 h. The catheter was removed and participants returned at 24, 48, 72, and 96 h for additional blood. Albumin and SHBG were measured at time 0, 24, 48, 72, 96 h.

The body size measurements used were total body weight (BW), body adiposity index (BAI, [7]), body surface area (BSA, [8]), and body mass index (BMI, [9]) according to:

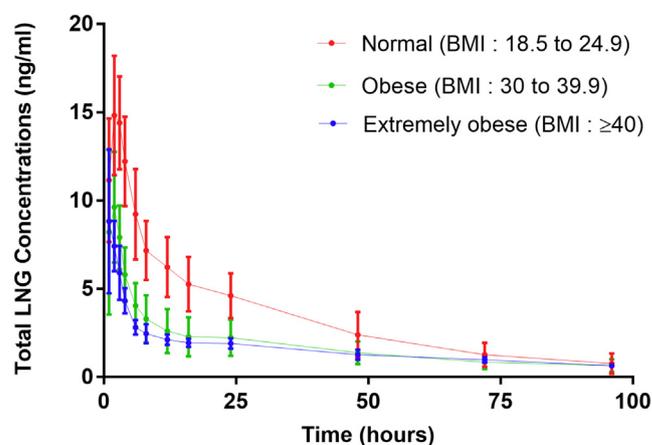$$\text{BAI } (\%) = \frac{\text{Hip circumference (cm)}}{\text{Height (m)}^{1.5}} - 18 \qquad (1)$$

Fig. 1. Concentration-time profiles of mean total LNG by BMI group.

$$\text{BSA } (\text{m}^2) = \text{Weight (kg)}^{0.425} \times \text{Height(cm)}^{0.725} \times 0.007184 \qquad (2)$$

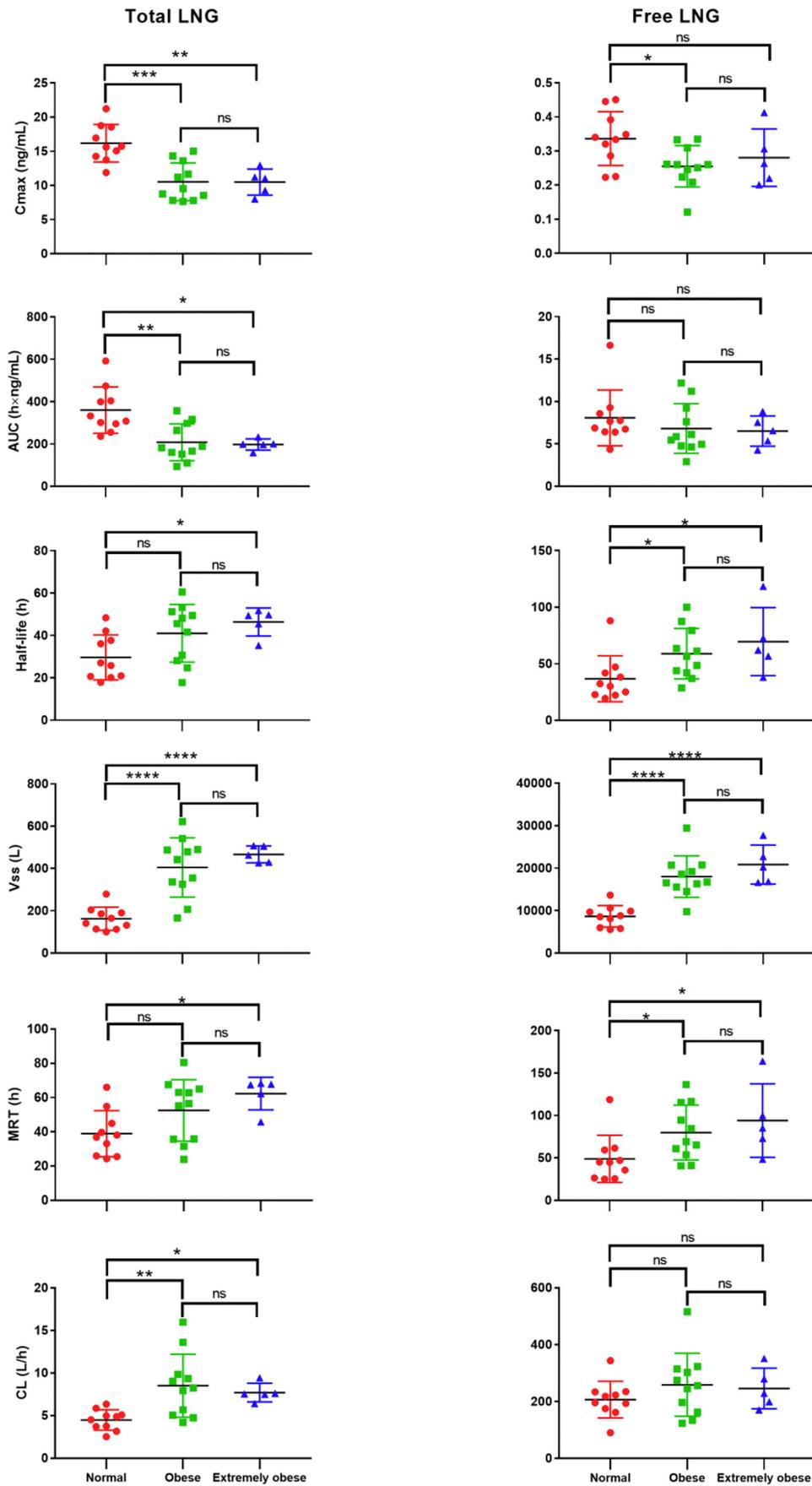$$\text{BMI } (\text{kg/m}^2) = \text{Weight (kg)}/\text{Height}^2 \text{ (m)} \qquad (3)$$

2.2. Sample size

The difference in LNG *Cmax* concentration between normal and obese subjects observed by Edelman et al. [10] was 0.6 ng/ml. However, with three groups planned, a more conservative difference was used. We expected 80% power to detect a difference of 0.36 ng/ml in LNG *Cmax* within the three groups assuming an alpha level of 0.05 and 10 subjects per group.

2.3. Bioanalytical methods

Serum LNG was quantified in serum by a specific and sensitive radioimmunoassay (RIA) [10,11]. Prior to RIA, LNG was extracted with hexane: ethyl acetate (3:2) to remove potential interfering conjugated steroids. Highly specific antisera were used in conjunction with an iodinated radioligand. Separation of free from antiserum-bound LNG was achieved by use of a second antibody. The sensitivity of the LNG RIA is 0.05 ng/mL. Intra- and inter-assay coefficients of variation (CV%) were 4.4% and 8.9%.

Serum SHBG and progesterone were measured by a solid-phase, two-site chemiluminescent immunometric assay on the Immulite analyzer (Siemens Healthcare Diagnostics, Deerfield, IL). The analytical sensitivity

Table 1
Demographic characteristics of the participants by BMI group

	Normal BMI (n=10)	Obese BMI (n=11)	Extremely obese BMI (n=5)
Age (years)	26.3 (18.0–34.0)	24.4 (18.0–31.0)	30.0 (23.0–34.0)
Ethnicity			
Hispanic	2 (20%)	7 (63.6%)	2 (40%)
African-American	3 (30%)	4 (36.4%)	3 (60%)
Asian	3 (30%)	0 (0%)	0 (0%)
Caucasian	2 (20%)	0 (0%)	0 (0%)
Weight (kg)	54.9 (45.6–61.7)	93.0 (81.8–108.6)	120.7 (103.6–151.3)
Body Mass Index (BMI) (kg/m^2)	22.0 (18.5–24.9)	34.4 (30.0–37.2)	46.6 (40.5–55.2)
Hip circumference (cm)	89.60 (82.00–96.00)	116.7 (107.5–124.0)	141.6 (135.0–158.5)
Body Adiposity Index (BAI) (%)	27.2 (19.6–31.1)	37.5 (33.2–44.3)	51.6 (42.4–57.0)
Body Surface Area (BSA) (m^2)	1.55 (1.37–1.65)	1.99 (1.79–2.19)	2.19 (1.97–2.46)

Normal BMI (18.5–24.9 kg/m^2), obese BMI (30–39.9 kg/m^2), extremely obese BMI (≥ 40 kg/m^2).
Values are reported as mean and total range.
Ethnicity is self-reported, presented as n(%).

Fig. 2. Comparison of the mean noncompartmental PK parameters for total and free LNG by BMI group. Normal BMI (18.5–24.9 kg/m^2), obese BMI (30–39.9 kg/m^2), extremely obese BMI (≥ 40 kg/m^2) Pk parameters include maximum concentration (*Cmax*), the time to *Cmax* (*Tmax*), the area under the concentration versus time curve (*AUC*), half-life (*t*1/2), clearance (*CL*), mean residence time (*MRT*), and volume of distribution at steady-state (*Vss*) Horizonal bars depict statistical comparisons (*p<.05, **p<.01, ***p<.001, **** p<.0001).

for SHBG was 0.02 nmol/L and inter-assay CV% was <8%. Assay sensitivity for progesterone was 0.1 ng/ml and inter-assay CV% was <11%.

2.4. Calculation of free and bioavailable LNG concentrations

The measured concentrations of sex hormone binding globulin (SHBG) and albumin (Alb) in each subject and each time were used to calculate the free and bioavailable LNG concentrations for the measured LNG concentrations using the Vermeulen method as described in the Supplemental Materials [12–14].

2.5. Pharmacokinetics

Noncompartmental Analysis (NCA) was used for assessment of the serum LNG concentration versus time profiles. The individual maximum concentration (*Cmax*) and the time to *Cmax* (*Tmax*) were observed values. The area under the concentration versus time curve (*AUC*), half-life (*t*1/2), clearance ($CL = \frac{Dose}{AUC}$), mean residence time (*MRT*), and volume of distribution at steady-state ($Vss = CL \times (MRT - \frac{Tmax}{2})$) were obtained using the Phoenix WinNonlin version 7.0 (Certara; Pharsight, St. Louis, MO). The linear-up log-down method was used for *AUC* values with extrapolations based on terminal half-lives. The software R was applied for ANOVA if the data were parametric; otherwise the Kruskal-Wallis method was used to assess differences between weight groups. The Tukey test was used for pairwise assessments following ANOVA and the Dunn test was used after Kruskal-Wallis analyses.

3. Results

The demographic characteristics of the participants are summarized in Table 1.

Fig. 1 provides the mean concentrations of total LNG versus time for the three groups of women who received 1.5 mg tablets. Serum LNG concentrations are consistently higher in the women of normal BMI and lowest in the extremely obese group. Absorption occurred rapidly producing a sharp peak at about 2 h followed by a biexponential decline with a long terminal half-life typically averaging 30 to 46 h over the 96-h sampling period.

The descriptive and NCA pharmacokinetic parameters for both total and free LNG are shown in Fig. 2 for the three groups. The arithmetic mean (SD) values of PK parameters are listed in Table 2. Both arithmetic and geometric means were calculated and were very similar (not

Table 2
Summary of total and free LNG PK parameters for each BMI group

Parameters (U)	Normal BMI $n=10$	Obese BMI $n=11$	Extremely obese BMI $n=5$
Total LNG			
Cmax (ng/mL)	16.2 (2.8)	10.5 (2.8)	10.5 (1.9)
Tmax (h)	2.5 (2.0–3.0)	2.0 (1.0–2.0)	1.0 (1.0–2.0)
AUC (h × ng/mL)	360.1 (109.3)	208.1 (87.0)	197.8 (26.5)
*t*1/2 (h)	29.7 (10.6)	41.0 (13.6)	46.4 (6.6)
Vss (L)	162.2 (54.6)	404.7 (140.2)	466.4 (39.6)
MRT (h)	39.0 (13.4)	52.5 (17.9)	62.3 (9.6)
CL (L/h)	4.48 (1.19)	8.51 (3.71)	7.70 (1.09)
Calculated free LNG			
Cmax (ng/mL)	0.337 (0.079)	0.255 (0.061)	0.281 (0.084)
Tmax (h)	2.5 (2.0–3.0)	2.0 (1.0–2.0)	1.0 (1.0–2.0)
AUC (h × ng/mL)	8.07 (3.29)	6.81 (2.92)	6.51 (1.79)
*t*1/2 (h)	36.8 (20.2)	59.0 (22.3)	69.6 (30.1)
Vss (L)	8664 (2511)	18,013 (4907)	20,844 (4597)
MRT (h)	49.0 (27.8)	79.9 (32.3)	94.1 (43.4)
CL (L/h)	206.9 (64.6)	258.9 (110.8)	245.7 (71.7)

Pk parameters include maximum concentration (*Cmax*), the time to *Cmax* (*Tmax*), the area under the concentration versus time curve (*AUC*), half-life (*t*1/2), clearance (*CL*), mean residence time (*MRT*), and volume of distribution at steady-state (*Vss*).
Values are reported as arithmetic mean (SD); *Tmax* is reported at median (Q1-Q3).

shown). For total LNG, the *Cmax* in both obese groups were significantly lower than in normal as can also be seen in Figs. 1 and 2. The *AUC* values were also lower in the obese groups when compared to normal. However, these exposure parameters as calculated for free LNG were actually much closer in the three groups. The non-normalized *Vss* (in L) was significantly larger in the obese groups (405 and 466 vs. 162 L, both p<.0001) when calculated for total LNG and also much larger in the obese groups for free LNG. The half-life values were significantly longer for obese subjects when based on both total (41 and 46 vs. 30 h, NS and p<.05) and free LNG (59 and 70 vs 37 h, both p<.05). The *MRT* values differed similarly.

3.1. Serum protein concentrations

The initial and day-4 SHBG and albumin concentrations are shown in Fig. 3 in the three groups. At initial dosing, significantly lower concentrations of SHBG were found for extremely obese compared to normal-BMI individuals (27.6 vs. 55.4 nmol/L, p=.037). Differences in SHBG were also seen at times 24, 48 and 72 h between the groups. The SHBG concentrations were similar for obese and extremely obese subjects.

The SHBG and albumin concentrations decreased after the dose of LNG. After 4 days, the mean decline from pre-LNG values of SHBG was 27.6% for normal weight, 30.8% for obese, and 25.9% for extremely obese subjects (with exclusion of one outlier who had an increase in SHBG) for subjects who had values on days 1 and 4. Corresponding changes for albumin were 35.2%, 34.5%, and 34.7%. Paired t-tests showed that the overall concentrations at 96 h were lower than at 0 h for SHBG (p=.0174) and albumin (p<.001).

Use of the Vermeulen computational method, our measured concentrations of LNG, SHBG and albumin, and the assumptions about binding values for the two proteins yielded free fractions of LNG of about 2.10% in normal weight, 2.66% in obese, and 2.65% in extremely obese subjects. As shown in Fig. 3, with the decrease of SHBG with body weight, there was an increase in the free fraction of LNG. The *AUC* of free LNG was fairly constant with weight, but the bioavailable *AUC* decreased significantly.

Additional comparisons of the individual PK parameters for total and free LNG for the three groups are shown in Fig. 2. The increases (or lack thereof) in most parameters with body weights were confirmed. The values of *CL* differed for total LNG but were similar for free LNG in the three weight groups.

4. Discussion

Our study found serum concentration versus time profiles of total and bioavailable LNG with smaller *Cmax* and *AUC* values in women with BMI>30. However, the calculated free LNG *Cmax* and *AUC* were very close in the three groups. Interestingly, BMI did not impact the *Tmax* for total or free LNG. The larger *Vss* seen in the obese groups for both total and free LNG are consistent with the greater tissue mass for distribution of the drug. Accordingly, longer *t*1/2 and *MRT* values in these groups were observed as the larger distribution space results in longer retention of LNG in the obese women. Although *CL* was increased for total LNG, it was not affected for free LNG PK. The women with BMI >30 exhibited lower SHBG concentrations that accounted for differences in *CL* based on total versus free LNG.

For total LNG, a lower *Cmax* for obese subjects was also found by Edelman et al. [6] and by Praditpan et al. [5] where the same 1.5 mg dose of LNG was given. For free LNG, our *Cmax* was slightly lower in obese subjects (p=.0446), while Edelman et al. showed no difference in relation to body weight. A lower *AUC* of total LNG was also reported in obese subjects by Praditpan et al. [5] with sampling to 48 h, but the Edelman et al. [6] study was limited to the time frame of 0 to 2.5 h. Edelman et al. [6] included direct measurements of free LNG, which were greater in obese women owing to their lower SHBG concentrations
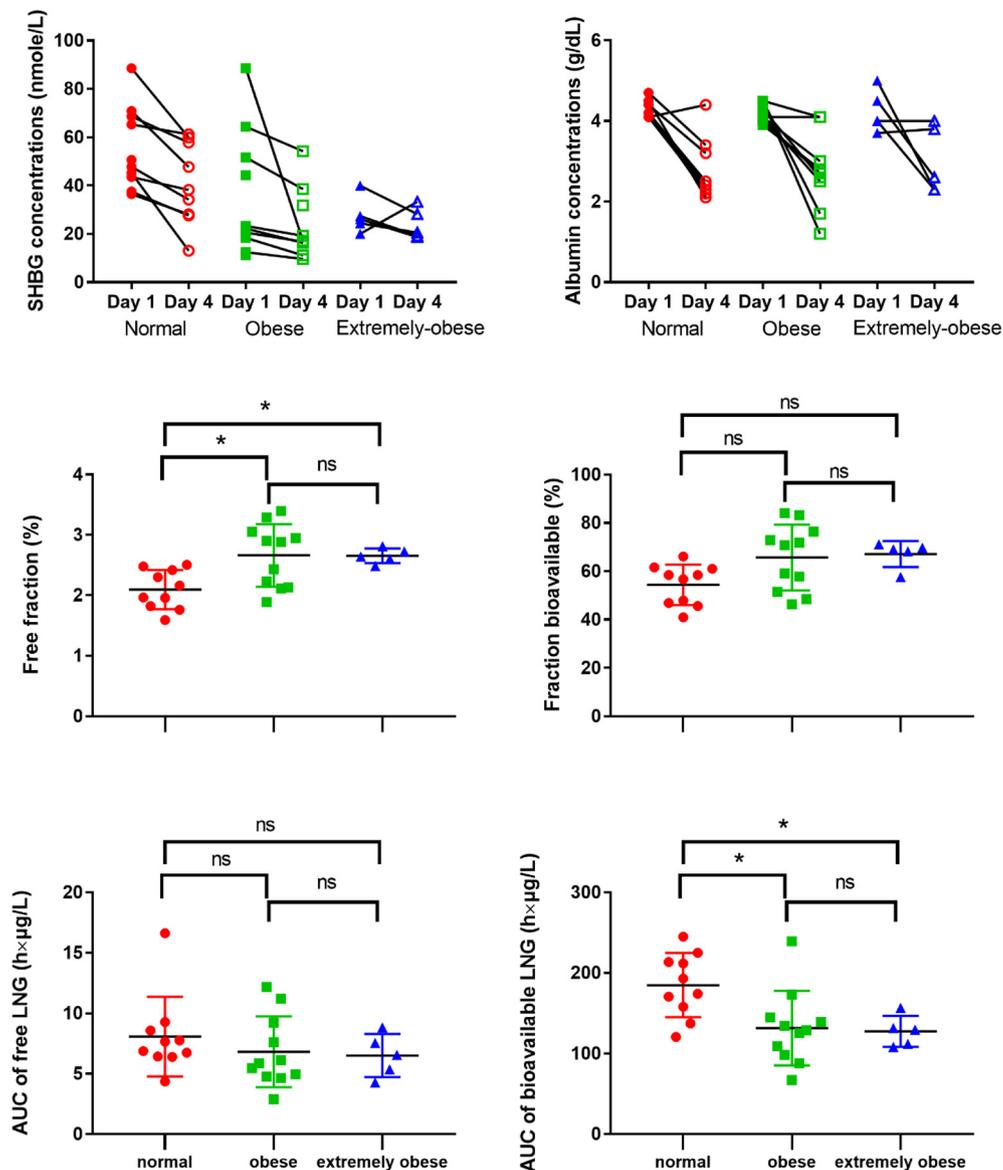
Fig. 3. Changes is SHBG and albumin concentrations over time by BMI groups and corresponding changes in mean free and bioavailable LNG percentage and AUC in relation in BMI.

with values in agreement with our calculations. The Praditpan and Edelman studies used LC/MS/MS for analyses, while our study employed a sensitive and specific RIA method.

Lower SHBG concentrations occur in obesity [6,15]. Additionally, decreases in SHBG after LNG exposure are well-known [16,17]. The mechanism of reduced SHBG with LNG is assumed to be decreased hepatic production. However, another factor may be internalization of the SHBG-LNG complex in target cells [18]. After implantation of LNG via Norplant there was a reduction of 19% in SHBG at day 3 and 60% at day 7 [16]. After placement of an intrauterine device containing LNG, there was an initial decline and then SHBG was stable over the ensuing 36-months [19]. With a single-dose of 1.5 mg LNG-EC, SHBG concentrations fell by 36% after 5 days [17]. Our findings were similar with about 30% decreases in both SHBG and albumin after 4 days. Kuhnz et al. [20] also described reductions in SHBG during daily oral dosing of 0.15 mg LNG.

Both SHBG and albumin concentrations decreased in all LNG study groups (Fig. 3). There appear to be no previous reports of changes in plasma albumin during use of LNG alone. While Amatayakul et al. showed decreased albumin after OC use, the estrogen is a complication

[21]. Kuhnz et al. [20] originally described increases in free LNG during daily dosing with 0.15 mg and demonstrated the shared binding of LNG to both SHBG and albumin.

Several contraceptive progestins given by various routes of administration exhibit modestly (about 30%) lower total serum concentrations in obesity [22].

LNG has a low hepatic extraction ratio of 0.12–0.14 (Table I from Kuhnz [23]) indicating that, like most drugs, uptake and metabolism of the drug by the liver is likely governed by free drug in plasma. Thus, the free drug clearance primarily controls the exposure, or *AUC*, of free drug. However, metabolism of LNG by adipose tissue is possible as indicated by numerous genes for drug metabolizing enzymes found in fat [24,25].

The changes in distribution kinetics of LNG in obesity are quite interesting. The logP of LNG is between 3.25 and 3.8, indicative of a moderately lipophilic drug. Nilsson et al. [26] measured LNG in fat tissue and found a fat to plasma ratio of 7.9. Most lipophilic drugs are distributed preferentially into adipose tissue resulting in increased volumes of distribution [24]. Moreover, with the lower SHBG concentration and higher free fraction in obesity, LNG is readily able to diffuse out of blood. The increased tissue mass and access of free drug accounts for the much

larger V_T and V_{ss} and longer half-life in the obese subjects. This behavior was similar for thiopental, which has a logP of about 3 [27]. Cardiac output [28] and blood flow to adipose tissue [29] also increase in obesity.

A variant of SHBG exists that decreases the affinity to testosterone causing an increase in the free fraction [30]. Perhaps the higher LNG clearances found for two individuals in this study was due to this factor. Studies of the PK of a larger number of obese women are needed to determine if these two subjects were either outliers or a subgroup with genetic differences.

The strengths of this study include the extensive LNG venous sampling which allowed for more accurate calculation of drug exposure. We included extremely obese women in whom we would expect the additional adipose tissue would induce greater distribution and metabolic changes.

There were some limitations in this study. Values of free LNG were obtained by calculation rather than measurement. However, our calculated values of free LNG for normal women are consistent with directly measured values previously published (Table S-1) and found recently by Edelman et al. [6].

The bioavailability was assumed to be complete (F=1) and similar in all groups. Studies of the PK of various drugs in obesity have not reported any problems with drug absorption [24].

How do these results relate to the concerns that use of 1.5 mg doses of LNG for EC may be less efficacious in obese women? There is no clear consensus on this issue [3,4]. The interpretation of our findings is somewhat dependent on whether the "free hormone hypothesis" is relevant in relation to PK and efficacy. This hypothesis poses that only free drug in plasma is available for both clearance and uptake into tissues. There is support for this [14], but there are also cell and preclinical studies that suggest an uptake mechanism for the SHBG-LNG complex into target cells via megalin [31]. If the free hormone hypothesis operates, then the similarities in free CL and free $Cmax$ and AUC suggests that obese women should not have impaired contraception efficacy. However, recent considerations in regard to measuring total versus free testosterone have led to preference for the free 'bioavailable' hormone as the active moiety [14] that is available to target sites. Notably, we found that the AUC of 'bioavailable' (free plus albumin-bound) LNG is significantly lower in obese women (Fig. 3). If target tissue uptake is controlled by the bioavailable LNG concentrations, this would explain the possible reduced efficacy of LNG in obese women. Our subsequent report will describe the ovulation rates and other clinical aspects of this study.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.contraception.2019.01.003.

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