GENERAL GYNECOLOGY

Pharmacokinetics of the etonogestrel contraceptive implant in obese women

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OBJECTIVE: We sought to examine the pharmacokinetics and acceptability of the etonogestrel contraceptive implant in obese women.

STUDY DESIGN: We developed and validated a plasma etonogestrel concentration assay and enrolled 13 obese (body mass index ≥30) women and 4 normal-weight (body mass index <25) women, who ensured comparability with historical controls. Etonogestrel concentrations were measured at 50-hour intervals through 300 hours postinsertion, then at 3 and 6 months to establish a pharmacokinetic curve.

RESULTS: All obese participants were African American, while all normal-weight participants were white. Across time, the plasma etonogestrel concentrations in obese women were lower than published values for normal-weight women and 31-63% lower than in the normal-weight study cohort, although these differences were not statistically significant. The implant device was found highly acceptable among obese women.

CONCLUSION: Obese women have lower plasma etonogestrel concentration than normal-weight women in the first 6 months after implant insertion. These findings should not be interpreted as decreased contraceptive effectiveness without additional considerations.

Key words: contraception, implantable devices, obesity, pharmacokinetics

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Nearly one-third of Americans aged ≥20 years are clinically obese,[1] having body mass index (BMI) ≥30.0 kg/m^2. Obese women are at increased risk of pregnancy complications such as gestational diabetes, respiratory problems, hypertension, and preeclampsia, and at higher risk of poor obstetrical/neonatal outcomes including increased likelihood of cesarean delivery.[2,3] Addressing family planning needs of obese women is of clinical and public health importance.

Providing contraception to obese women poses challenges due to concerns about potential decreased efficacy with combined hormonal contraceptive methods and concerns about increased risk of venous thromboembolism compared to normal-weight women when taking estrogen-containing contraceptives.[3-6] Given these issues, the American Congress of Obstetricians and Gynecologists has encouraged clinicians to consider use of highly effective, long-acting progestin-only contraceptives and implantable devices in obese women.[7]

As yet, there are limited data available for the etonogestrel contraceptive implant in obese women, as phase II and III clinical trials did not include women who exceeded 130% of ideal body weight.[8] Yet, there is reason to suspect that the pharmacokinetic profile of the etonogestrel contraceptive implant is affected by body mass. An inverse relationship between plasma etonogestrel concentration and body weight in etonogestrel contraceptive implant users has been described.[9] A cross-sectional analysis of etonogestrel serum levels taken just prior to implant removal in 1063 women adjusted for the duration of use, extrapolated over 3 years of use, and stratified by body weight category showed a weight-related trend in serum concentrations, with highest concentrations at <50 kg and lowest concentrations in the ≥70 kg group.[9] The only published prospective data come from a case series (n = 3) of morbidly obese (BMI 51.8-64.7 kg/m^2) women initiating the contraceptive implant 1-2 months before bariatric surgery.[10] Etonogestrel concentrations, measured before and after surgery at various time points up to 8 months postinsertion, were lower than those observed in normal-weight historical controls.

Given this knowledge gap, this paper describes the pharmacokinetics of the etonogestrel contraceptive implant in obese women during the first 6 months of use and provides data on the acceptability, side effect profile, and ease of palpation in these women.

Materials and Methods

Study medication

The etonogestrel contraceptive rod is an implantable device consisting of 68 mg

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of etonogestrel as the active ingredient with an average release rate of 60-70 μg/d in weeks 5-6, decreasing to approximately 35-45 μg/d by year 1, 30-40 μg/d by year 2, and then to 25-30 μg/d at the end of the third year.[11] The bioavailability remains constant and close to 100%, and the elimination half-life of the parent compound is around 25 hours.[9] Etonogestrel is mainly bound to albumin, which is not affected by changes in body's serum estrogen levels. There is no serum accumulation; the steady decline in concentration is due mainly to the slightly declining release rate over time.[12]

Study procedures

This observational pharmacokinetic study was conducted at the University of Chicago Medical Center in collaboration with the University of Washington from June 2008 through September 2009. Institutional review board (IRB) approval was obtained at both institutions for the duration of the study. An IRB-approved flier was developed by study staff for participant recruitment. Fliers were posted at the University of Chicago Obstetrics and Gynecology outpatient medical clinics and in various community-based locations on the south side of Chicago, IL. An IRB-approved online advertisement was also posted to Craigslist and on the University of Chicago Intranet World Wide Web site. Participants were all self-identified. Interested participants then spoke with a study staff member via telephone to discuss study protocols and complete a basic eligibility screening. All eligible women were invited to a screening and enrollment visit. Nineteen women were screened and of those, 17 remained interested and eligible. Informed consent was then obtained from all participants in accordance with standard human subjects protection guidelines. Two cohorts of women were enrolled: women with BMI ≥30 (obese women)[13] and a smaller cohort of women with BMI <25 (normal-weight women). Normal-weight women were enrolled to compare their pharmacokinetic parameters to those of normal-weight historical controls, aiding in the validation of the etonogestrel assay developed for this study. Women aged 18-45 years were included in the study if they were in general good health, met BMI criteria, were premenopausal with a uterus and at least 1 ovary, were willing to comply with the study protocol and visit schedule, were weight stable/not interested in gaining or losing weight during the study period, and had regular menses with monthly moliminal symptoms over the year prior to participation. Women were excluded if they had any contraindication to use of the implant, were breast-feeding, had a known or suspected pregnancy, were planning a pregnancy within 12 months, or had a delivery or abortion within 4 months of device insertion. Other exclusion criteria included: abnormal genital bleeding, hypersensitivity or allergy to any components of the implant, or a history of polycystic ovarian syndrome, thromboembolic issues, liver disease, diabetes, glucose abnormality, >1 cardiovascular risk factor, or known medical contraindications. Women were excluded if they had used a cytochrome P450 3A4 inducer within 2 months, a cytochrome P450 3A4 inhibitor within 2 weeks, an investigational drug within 2 months, or injectable contraception within 6 months of the start of the trial medication.

Consistent with prior studies, we used a washout period of 14 days for women who were current combined hormonal contraceptive users.[14] Participants were advised to use a backup nonhormonal form of contraception or abstain from intercourse throughout the washout period.

All women who met study criteria were asked to participate. After a urine pregnancy test was confirmed negative, height and weight were measured, BMI was calculated, and vital signs were obtained, participants underwent standard insertion of the implant. All insertions were performed by a single physician who had completed company-required Implanon (Organon, Whitehouse Station, NJ) insertion training. Insertion took place during days 1-5 of the menstrual cycle. If deviating from the preferred timing of device insertion, insertion took place only if the participant had abstained from intercourse since the last menstrual period.

As peak serum concentration is usually achieved between 96-144 hours after the insertion of the device in normal-weight women (range, 24–263 hours), blood samples were obtained at 50-hour intervals until 300 hours (6 blood draws over 13 days) postinsertion for plasma etonogestrel concentration determination.[15,16] Two additional samples were obtained at 3 and 6 months postinsertion in the obese cohort to assess pharmacokinetics after the postdistributive phase. At all postinsertion visits, we measured blood pressure and weight, calculated BMI, asked about bleeding changes, evaluated the implant site, and described ease of device palpation.

Obese participants were asked to respond to a staff-administered survey regarding acceptability at the 300-hour, and the 3- and 6-month postinsertion visits. For participants requesting implant removal, the reason for discontinuation was documented. All participants were given the option of keeping the device for the full 3 years of use.

Laboratory procedures for developing etonogestrel assay

Serum and plasma samples were collected by venipuncture at the University of Chicago Medical Center in regular plasma tubes (green top; heparinized tubes). The vials of blood were centrifuged at 5000*g* for 10-15 minutes and plasma extracted into microcentrifuge tubes. Samples were stored at our site at −80°C and then bulk-shipped in dry ice to the University of Washington School of Pharmacy pharmacokinetic laboratory, where samples remained frozen at −80°C until the assays were performed.

Total plasma concentrations of etonogestrel were determined using a modification of an extraction, derivatization, and liquid chromatography-tandem mass spectrometry protocol as described by Kalhorn et al[17] for the measurement of testosterone. Briefly, 50 μL methanol containing testosterone-16,16,17-d_3 (Sigma Aldridge, St. Louis, MO) as an internal standard was added to screw-capped tubes and the methanol evaporated under nitrogen gas. In all, 100 μL of plasma samples were added. Samples were extracted twice with 5

mL of 80:20 hexane:ethyl acetate and dried under nitrogen gas. To form the oxime derivatives of etonogestrel and testosterone for liquid chromatography-mass spectrometry detection, the samples were reconstituted with 100 μL of 0.1 mol/L hydroxylamine hydrochloride (in 50:50 methanol:water) and transferred to autosampler vials with conical glass inserts. Samples were heated at 60°C for 1 hour. A final volume of 20 μL was injected onto a Waters Acquity UPLC coupled with a Micromass Premiere-XE tandem quadrupole mass spectrometer operated in the ES+ mode equipped with a Waters BEH C8 50 × 2.1 mm column (Waters Corp., Milford, MA). Column flow was 0.3 mL/min with a gradient starting at 95% water and 5% acetonitrile, changing to 10% water and 90% acetonitrile at 3 minutes. The column was rinsed at 100% acetonitrile and returned to 95% water and 5% acetonitrile at 4.2 minutes. Run time was 5.5 minutes. The oximes of 3D-testosterone eluted at 2.5 minutes, and etonogestrel at 2.8 minutes. Daughter ions (m/z) 112.1 and 124.1 of the precursor ion (m/z) 307.2 were monitored for the 3D-testosterone internal standard using a cone voltage of 50 and collision energy of 30 eV. The daughter ion (m/z) 124.1 of the precursor ion (m/z) 340.2 was monitored for etonogestrel using a cone voltage of 40 and collision energy of 30 eV. The range of quantitation for this assay was 100-2000 pg/mL. Quality control specimens were run each day. Intraday coefficients of variation were 4.9%, 3.7%, and 5.8% and interday coefficients of variation were 12.5%, 11.1%, and 11.0% for 500, 1000, and 1500 pg/mL levels, respectively.

Sample size

For this descriptive study, we calculated our sample size to allow for the characterization of the pharmacokinetic curve for etonogestrel concentrations in a previously unstudied population (ie, obese women). Similar published pharmacokinetic studies were of comparable size.[14,18,19] Due to the existence of ample historical data on normal-weight women, we did not power this study to produce a robust pharmacokinetic curve for the normal-weight cohort or make statistical comparisons between the normal-weight and obese participants.

TABLE 1
Participant demographics

Demographic	Obese (n = 13)	Normal weight (n = 4)
Median age, y (range)	21 (18–40)	27 (21–30)
Race/ethnicity		
African American	13	0
White	0	4
Median BMI, kg/m^2 (range)	41 (33–52)	20 (19–22)
Median weight, lb (range)	233 (199–362)	113 (103–130)

BMI, body mass index.

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Determination of pharmacokinetic parameters

Serial plasma etonogestrel concentrations were plotted in a concentration-time curve based on the actual plasma etonogestrel concentration from each individual (the data are expressed as mean ± SD). The following pharmacokinetics parameters of etonogestrel were obtained directly from the measured results: peak plasma concentration (C_{max}) and time to achieve C_{max}. The area under the plasma concentration-time curve in the first 6 months was calculated using the trapezoidal rule in both groups. In the control group, the plasma etonogestrel concentrations at 3 and 6 months were modeled based on each patient's plasma concentrations up to 300 hours by linear regression analysis using data points obtained after C_{max} under the assumption that etonogestrel elimination follows first-order kinetics. Based on data from the manufacturer as well as a previously published pharmacokinetic study, the elimination phase of etonogestrel in the implant fits characteristics of first-order kinetics.[11,14] Additionally, the systemic clearance of the etonogestrel in the first 2 years after implantation remains around 7.5 L/h, further suggesting first-order kinetics.[9] Therefore, linear regression analysis of the log concentrations in the descending phase was used to estimate a rate elimination constant and extrapolate concentrations >6 months after implantation.

Statistical analysis

Descriptive statistics for baseline demographic and survey data were used to characterize the study population with frequencies and medians provided as appropriate. Statistical analyses were performed using STATA 9 (StataCorp LP, College Station, TX) and SigmaPlot (Systat Software, Chicago, IL). Concentration-time curve was created by using SigmaPlot (v.11.1).

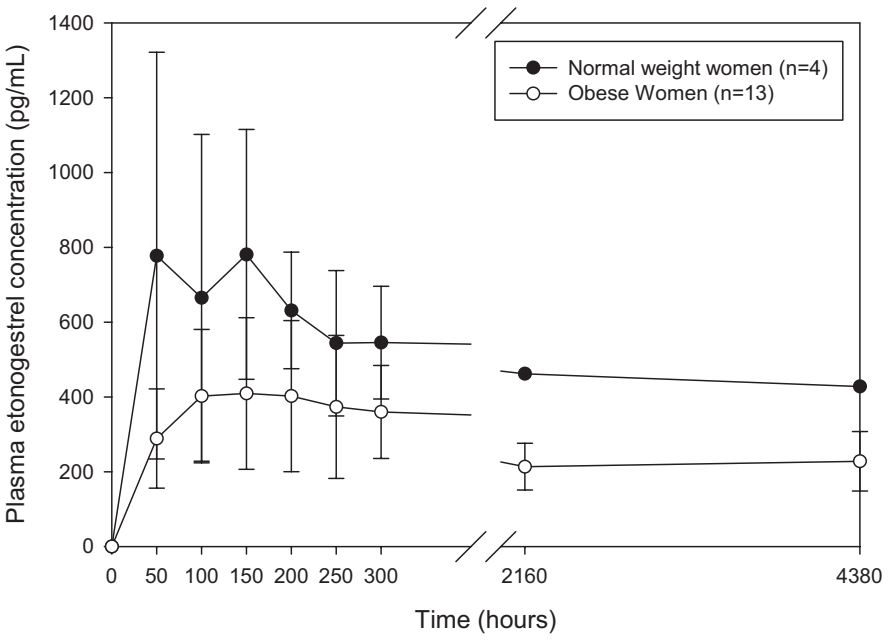
RESULTS

From June 2008 through March 2009, we screened 20 women (who self-classified as obese or normal weight). Of these, 17 were eligible and enrolled in the study. Within the overall enrolled cohort, 13 women met criteria for the obese cohort and 4 women for the normal-weight cohort. Table 1 describes further demographic characteristics for these 2 participant groups. For the obese cohort, the group of interest, the median BMI was 41 with a range of 33-52. The median weight was 233 lb (range, 199–362 lb) and the median age was 21 (range, 18–40 years). All obese participants were African American. BMI remained stable in the obese cohort; weight measurements fluctuated not >4 lb between the 3- and 6-month visits.

Pharmacokinetic results

The plasma concentration-time profile for etonogestrel in the normal-weight subjects closely resembled the data available in the manufacturer's package insert and published pharmacokinetic reports.[9,11,14,20,21] Among our normal-weight participants the peak etonogestrel concentration was 781 ±

FIGURE
Changes in etonogestrel plasma concentration over time



Sample sizes listed are for time of insertion (T = 0). For obese women, sample sizes at 300 hours, 3 months, and 6 months were n = 11, n = 8, and n = 8, respectively.

Mornar. Implanon pharmacokinetics in obese women. Am J Obstet Gynecol 2012.

334 pg/mL, achieved 150 hours (6.25 days) after insertion. We observed the same time to achieve C_{max} in our obese cohort. However, plasma etonogestrel concentrations in obese women at all measured time points were lower than previously published values for normal-weight women, as well as the values observed in our normal-weight cohort. The average C_{max} in obese women was 47.6% lower than that observed in normal-weight women (409 vs 781 pg/mL; $P = .11$). The average plasma etonogestrel concentrations in the postdistributive phase were between 31-54% lower for obese compared to normal-weight women. Mean etonogestrel concentrations for obese women at 3 and 6 months were 213.5 ± 62.5 pg/mL and 227.9 ± 79.5 pg/mL, respectively. As a result, the mean area under the plasma concentration-time curve from the time of device insertion to 300 hours postinsertion was 47.8% lower in the obese group compared with controls (95,871 ± 46,230 vs 183,603 ± 72,956 pg · h/mL; $P = .09$). Accordingly, etonogestrel exposure over the 3-year period in obese women is estimated to be 40% lower than in normal-weight women. Projected plasma concentrations at 1, 2, and 3 years after device insertion in the obese women were 133, 102, and 98 pg/mL, respectively.

The Figure represents the mean plasma concentration-time curve of etonogestrel in the obese cohort (n = 13) compared to the normal-weight group (n = 4) in the current investigation.

TABLE 2
Acceptability of contraceptive implant to obese participants

Variable	300 h (n = 11)	3 mo (n = 8)	6 mo (n = 8)
Satisfaction with implant			
Satisfied or very satisfied	9 (82%)	7 (88%)	8 (100%)
Neutral	2 (18%)	1 (12%)	0
Dissatisfied or very dissatisfied	0	0	0
Would recommend implant to a friend			
Agree or strongly agree	11 (100%)	7 (88%)	8 (100%)
Undecided	0	1 (12%)	0
Disagree or strongly disagree	0	0	0

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Acceptability and clinical experience analysis

There were 3 early terminations, all of which occurred in the obese cohort. Two participants terminated simultaneously at 6 weeks postinsertion; one reported bleeding concerns and the other stated a desire to become pregnant. A third participant terminated at the 3-month visit for bleeding concerns. Two participants, also from the obese cohort, were lost to follow-up prior to the 300-hour visit. All devices were palpable by provider and participant postinsertion and at the 3- and 6-month follow-up visits. Fourteen participants reported "none" and 3 participants reported "mild" pain with insertion. As Table 2 indicates, a majority of women in the obese cohort were highly satisfied with the device and would recommend to a friend.

Adverse events were tracked for all women up to 300 hours and for obese participants at 3 and 6 months additionally. The most commonly reported events across all time points were pain/irritation/itching at insertion site, bleeding/spotting, and headaches. Specifically, within the first 300 hours, 14 (82%) noted pain/irritation/itching at the insertion site, 6 (35%) reported bleeding/spotting, and 4 (23.5%) reported headaches. Other adverse events within the first 300 hours included: hot flashes/night sweats, cramping, mood changes, stomach pain/nausea, and breast swelling/tenderness. At 3 months (n = 8), 2 participants (25%) reported bleeding/spotting and 1 participant (12.5%) reported headaches. One participant also reported adverse events of hot flashes/

night sweats, swelling in extremities, and weight gain. At 6 months (n = 8), 1 participant (12.5%) reported headaches and 1 (12.5%) reported fatigue. There were no serious adverse events.

COMMENT

This study describes the pharmacokinetics and acceptability of the etonogestrel contraceptive implant in obese women during the first 6 months of use. We further considered absorption kinetics in normal-weight women. Results from our normal-weight cohort were consistent with previously published pharmacokinetic studies,[9,14] indicating that our etonogestrel assay was sensitive and accurate. These studies have observed mean peak serum etonogestrel concentrations peaking approximately 6 days after insertion (range 781-894 pg/mL) then gradually decreasing over time.[9,14] Although the shape of the concentration-time curve of etonogestrel in our obese cohort was similar to that in the normal-weight cohort, the etonogestrel concentrations were consistently lower at each interval. While our study was not designed to identify statistically significant differences between our obese and normal-weight participants, the magnitude of the differences was striking and at times was borderline significant. These results are consistent with literature suggesting an inverse relationship between plasma etonogestrel concentration and body weight in implant users.[9] Our findings cannot be directly compared to the case series by Ciangura et al[10] given that their cohort was morbidly obese, was not weight stable, and contributed measurements at varying time points postinsertion. However, estimated etonogestrel concentrations at 6 months postinsertion for 2 of their 3 subjects (200-250 pg/mL) were in a similar range to what we found.

Existing data suggest that an etonogestrel concentration >90 pg/mL is necessary to effectively prevent ovulation.[22] In normal-weight women, the average etonogestrel concentration at 2 and 3 years postinsertion are 194 and 156 pg/mL, respectively. Our data showed that the average etonogestrel concentrations in obese women at the same time points are projected to be 102 and 98 pg/mL. This finding raises concern regarding the contraceptive effectiveness of the implant over time in obese women. In severely obese women, it is possible that ovarian suppression cannot be assured at 2 and 3 years postinsertion. The case series described by Ciangura et al[10] also indicates concern for contraceptive efficacy, as it includes a morbidly obese (preoperative BMI 64.7 kg/m^2) 24-year-old whose etonogestrel concentrations at 5 and 8 months postinsertion (approximately 3 and 6 months postsurgery) were only 134 and 125 pg/mL, respectively.

The study limitations must be noted. First, ours is a pharmacokinetic study and not a study of hormonal efficacy or contraceptive effectiveness. Thus, we present only 1 piece of information about the etonogestrel contraceptive implant in obese women. Future studies of the implant in obese women would determine the minimum plasma concentration of etonogestrel necessary for ovulation inhibition in this specific population, take into account the secondary mechanism of action for etonogestrel (ie, thickening of cervical mucus), and consider actual pregnancy rates. The racial homogeneity of our obese cohort may limit the generalizability of our findings to other racial/ethnic groups. Furthermore, the difference in racial composition between our 2 cohorts means that we cannot rule out the possibility that race contributed to the differences that we observed. Ours was a small study; as such, the small number of discontinuations and losses to follow-up were large in relative terms. Finally, our data are limited to 6 months of follow-up. Despite not being able to measure plasma etonogestrel levels near the end of the 3-year use period, we were able to extrapolate these data using pharmacokinetic modeling.

Nevertheless, this study is the first to report pharmacokinetic data in obese users of the etonogestrel contraceptive implant. In addition, we have developed a company-independent assay for etonogestrel that could be used in future studies of the implant. Overall, our study adds to the literature on the pharmacokinetics of the etonogestrel contraceptive implant in this important population. As women in this study found this method highly acceptable, they deserve more information about its effectiveness. ■

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