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A pilot study of levonorgestrel concentrations and bleeding patterns in women with epilepsy using a levonorgestrel IUD and treated with antiepileptic drugs☆,☆☆,★

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ABSTRACT

Objectives: We explored levonorgestrel (LNG) concentrations, bleeding patterns and endometrial thickness in women with epilepsy (WWE) initiating an LNG-intrauterine device (IUD) co-administered with antiepileptic drugs (AEDs).
Study design: This pilot study included 20 WWE ages 18 to 45 years with well-controlled seizures and stable AED regimens initiating a 52-mg LNG-IUD (20 mcg/d initial release). We collected blood and measured endometrial thickness before IUD placement and 21 days, 3 months and 6 months thereafter. Participants recorded bleeding/spotting daily. We measured total LNG (radioimmunoassay), serum hormone binding globulin (SHBG, immunoassay) and calculated the free LNG index. We compared total LNG, free LNG index, SHBG and endometrial thickness over time using a linear mixed-effects model.
Results: Total LNG, free LNG index and SBHG levels remained stable from day 21 throughout. Endometrial thickness decreased from a median of 5.9 mm [interquartile range (IQR) 4.6–7.5] at day 21 to 3.3mm (2.8–4.9) by month 6 ($p=0.02$). Bleeding and spotting days decreased from a median of 16 (IQR 13–23) in month 1 to 6.5 (IQR 4–8.5) in month 6 regardless of AED regimen.
Conclusion: Like women without epilepsy, WWE initiating the LNG-IUD experience stable total LNG concentrations and decreasing endometrial thickness and bleeding over the first 6 months of use.
Implications: Like women without epilepsy, WWE using antiepileptic drugs can expect a stable LNG concentration and decreasing bleeding during the first 6 months of LNG-IUD use. Our data can be useful for guidance of WWE considering use the LNG-IUD.

1. Introduction

Planning pregnancy is particularly important and complex for women with epilepsy (WWE) treated with antiepileptic drugs (AEDs). Co-administration of certain AEDs and hormonal contraceptives increases the risk of contraceptive failure and seizure exacerbation [1,2].

The levonorgestrel-releasing intrauterine device (LNG-IUD) is long-acting, reversible, effective and safe option, and user continuation and satisfaction rates are typically high [3–6]. The 52-mg LNG-IUD (20 mcg/d initial release) product label includes a warning of reduced efficacy with co-administered enzyme-inducing AEDs [7]. Co-administration of these drugs is unlikely to compromise LNG-IUD effectiveness, however, given its local mechanism of action [8,9], and limited data suggest that LNG IUS efficacy in WWE treated with AEDs remains high [1,10,11]. One small observational pilot study, however, did find a higher failure rate in 52-mg LNG-IUD (20 mcg/d initial release) users treated with enzyme-inducing AEDs [10]. Medical eligibility criteria for contraceptive use from the World Health Organization and the US Centers for Disease Control and Prevention state that LNG-IUD can be safely co-administrated with all AEDs [12,13].

Epilepsy can be hormonally sensitive. Beyond efficacy concerns, minimal safety and acceptability data are available to guide clinicians prescribing hormonal contraception for WWE. A recent prospective pilot study was reassuring; seizure control and AED concentrations

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remained stable during the 6 months after 52-mg LNG-IUD insertion, and satisfaction and continuation were high [11]. Limited clinical data in WWE may explain why one survey showed that less than 50% of the interviewed neurologists from a reference center for epilepsy in Brazil recommended LNG-IUD for AED users, regardless of the enzyme-inducer status [14].

Experiences from peer groups of LNG-IUD users may not be applicable to WWE treated with AEDs, and clinicians will benefit from information describing pharmacokinetic and pharmacodynamic changes after initiation. Our study aimed to explore serum LNG concentrations, endometrial thickness and bleeding patterns in WWE initiating the LNG-IUD with co-administered AEDs during the first 6 months of use. Additionally, we conducted this study to determine feasibility of a future, larger study in this special population.

2. Material and methods

2.1. Study design and settings

This pilot study included 20 WWE initiating an LNG-IUD (20 mcg/day) between 2011 and 2013 at Columbia University Irving Medical Center (CUMC) in New York City after approval by the CUMC Institutional Review Board. This clinical trial was registered (www.clinicaltrials.gov; NCT02362373).

2.2. Participants

We included women 18–45 years old with well-controlled epilepsy (≤2 seizures per month, more allowed if focal without awareness impairment) and regular menstrual cycles of 21–35 days choosing the LNG-IUD for contraception. We required a stable AED regimen without a change of AED dose or type during 2 months prior to enrollment. Exclusion criteria were short-acting hormonal contraceptive use in the month prior to enrollment, depot medroxyprogesterone acetate use in the 6 months prior to enrollment, medical contraindications to IUD use [13] or recent pregnancy. Participants provided written informed consent.

We categorized AED regimens into two groups: (1) inducer regimens included at least one enzyme-inducing AED and (2) noninducer regimens without an enzyme-inducing AED [12,15]. Enzyme-inducing AEDs included carbamazepine, oxcarbazepine and topiramate (>200 mg/day); non-enzyme-inducing AEDs included lamotrigine, levetiracetam, lacosamide, valproate, acetazolamide and clobazam [1,12,15].

2.3. Outcomes, measurements and study procedures

The primary outcomes were serum LNG concentrations and bleeding patterns in WWE during the 6 months after initiating the LNG-IUD, with endometrial thickness and sexual hormone binding globulin (SHBG) levels as secondary outcomes. We evaluated serum LNG concentrations by total LNG concentration and free LNG index, a proxy for unbound LNG [16,17]. We compared endometrial thickness, serum LNG concentration and SHBG levels between WWE using hepatic-enzyme-inducing ($n=5$) and noninducing AED regimens ($n=15$). We reported AED concentrations, seizure control, satisfaction and continuation separately [11].

Study staff administered a baseline questionnaire to record demographic characteristics, contraceptive history and medications. Participants' neurologists confirmed AED type and dose. Participants recorded seizures and menstrual bleeding in daily paper diaries for 1 month prior to LNG-IUD insertion. Participants returned within the first 7 days of the next menses for a transvaginal ultrasound (TVU) to measure endometrial thickness and LNG-IUD placement (Mirena®, Bayer, Whippany, NJ, USA). We performed venipuncture before placement for SHBG, LNG and AED concentrations.

For 6 months, participants recorded bleeding daily and returned on day 21 after placement and 3 and 6 months later. The 3- and 6-month visits were timed to occur on day 21 (±2 days) of each month. At each visit, we reviewed diaries, performed TVU and collected blood for SHBG, LNG and AED concentrations.

We centrifuged the blood and aliquoted serum for storage (−70°C). Syrinx Bioanalytics (Turku, Finland) evaluated total serum LNG concentration by radioimmunoassay (RIA), previously validated [18–21]. RIA uses competitive binding of unlabeled and tritium-labeled LNG to a specific antiserum preparation. Serum samples were extracted with diethyl ether before the RIA. LNG was measured using a liquid scintillation counter method. Samples were analyzed in duplicate in one run. The lower (LLOQ) and upper (ULOQ) limits of quantification of the assay were 30 ng/L and 600 ng/L, respectively with a calibration range of 10 to 2000 ng/L. A run was accepted when criteria for calibrators and controls were met. The calibration standards for LNG were as follows: (1) The precision [% coefficient of variation (CV)] of the duplicates was ≤15%. (2) The accuracy of all six calibration standards points within measurement range of 85%–115% of the nominal values (80%–120% at LLOQ). At least 50% of the duplicate samples within each quality control (QC) concentration and 4 out of 6 (67%) of all QC samples in a run had to fulfill the following criteria: (1) The precision (% CV) of the duplicates was ≤ 15%. (2) The accuracy (%) of QC results was 85%–115% of the nominal values. If criteria were unmet, the run was rejected and repeated.

If the precision (% CV) of duplicates for a LNG samples was >15%, the LNG result was rejected and the sample reanalyzed. Intraassay CVs for LNG RIA ranged from 2.6% to 5%. SHBG was evaluated by Syrinx Bioanalytics using a target-dependent dissociation enhanced lanthanide fluorescence immunoassay (DELFIA) method, previously validated [22]. This solid-phase, two-site, fluoroimmunometric method is based on a direct sandwich technique with two monoclonal anti-SHBG antibodies using automated AutoDELFIA equipment. All samples were analyzed in duplicate on 96-well microtitration plates in assays runs with an LLOQ and ULOQ of 10 nmol/L and 512 nmol/L, respectively, and a calibration range of 10 to 512 nmol/L. The intraassay CV for SHBG ranged from 3.4% to 7.4%, while interassay CV for SHBG ranged from 5.8% to 14.7%. We used immunoassay evaluation software (MultiCalc version 2.7) to calculate the standard curve parameters and quantitative analyte concentrations for LNG and SHBG.

Levonorgestrel is bound to SHBG with a high affinity and in this form is not biologically active. To assess unbound LNG, we calculated the free LNG index as the ratio between total LNG and SHBG [(LNG (nmol/L) / SHBG (nmol/L)) × 100] [16].

We instructed participants to record bleeding using the following code: (0) no bleeding; (1) spotting, defined as any bloody vaginal discharge not requiring sanitary protection; or (2) bleeding, defined as any bloody vaginal discharge requiring sanitary protection [23]. We characterized bleeding based on the World Health Organization's recommended definitions using the frequency and duration of the bleeding/spotting episodes in a 90-day reference period (RP) [23,24]. An episode was characterized by any bleeding/spotting days bounded on either end by 2 days of no bleeding or spotting [25]. The frequency of bleeding/spotting episodes was defined in each 90-day RP as (1) amenorrhea (no bleeding or spotting [B/S] episodes), (2) infrequent (<3 B/S episodes), (3) normal frequency (3–5 B/S episodes, representing the episodes expected in women with regular cycle) or (4) frequent (>5 B/S episodes). An episode was defined as prolonged if >14 days [23,24]. We summarized the number of bleeding and spotting days in each 30-day period from baseline to 6 months.

2.4. Statistical analysis

As a pilot study, we selected our sample size based on feasibility constraints. In addition to our primary descriptive outcomes, we planned to use our results as estimates to plan a larger study with sufficient

Table 1
Demographic and clinical characteristics of women with epilepsy included in the study

Characteristic	Mean (SD)
Age (years)	28.2 (6.2)
BMI (kg/m^2)	25.3 (3.5)
Cycle length (days)	28. 3 (1.9)
Menses' duration	5.3 (0.7)
Characteristic	***N* (%)**
Race	
White	16 (80%)
Other races[a]	4 (20%)
Education	
College	14 (70%)
Some or all graduate or professional school	6 (30%)
Smoking	2 (10%)
Having a relationship	14 (70%)
Parity	
0	12 (60%)
≥1	8 (40%)
Ever IUD user[b][c]	3 (15%)
History of dysmenorrhea	14 (70%)
AED regimen used	
With enzyme-inducing AED[c]	5 (25%)
Without enzyme-inducing AED	15 (75%)

BMI, body mass index; SD, standard deviation.
[a] African-American, mixed.
[b] All copper IUD users.
[c] Three oxcarbazepine users, one carbamazepine user and one topiramate (>200 mg) user.

participants to conduct adequately powered statistical comparisons, if feasible.

We used descriptive statistics to summarize bleeding patterns and demographic and clinical characteristics. We evaluated differences in participants' total LNG concentration, free LNG index, SHBG levels and endometrial thickness before and during 6 months after LNG-IUD insertion. For LNG concentration and free LNG index, we excluded the baseline zero value. For endometrial thickness, we excluded the baseline menstrual phase because other measurements were done on day 21. We compared these outcomes between WWE using inducer and noninducer AEDs. We used a linear mixed-effects model adjusted for multiplicity by Bonferroni correction. The level of significance was 5% for comparisons. We presented quantitative data as medians and associated interquartile range or means and standard deviations. We used SAS 9.4 (SAS Institute Inc., Cary, NC, USA) for analyses.

3. Results

Of 23 WWE screened, 20 WWE completed follow-up and were included in the analysis. We excluded three potential participants: one for poor seizure control; one who chose a different method of contraception; and in one, the IUD insertion failed. One endometrial thickness measurement was missing (day 21). Diaries were complete without missing data. Nineteen participants used condoms prior to enrollment; one used a copper IUD. Table 1 summarizes demographic and clinical data.

After LNG-IUD insertion, median total LNG concentration and free LNG index increased and remained stable from day 21 to 6 months (Table 2). Median SHBG levels decreased 13.6% from baseline to 3 months of LNG-IUD use (not statistically different) and remained stable until 6 months. The median endometrial thickness decreased 46% between day 21 and 6 months (p=.02) (Table 2). Considering the AED regimen in use, median SHBG levels were higher (ranging from 36% to 63%) in WWE using inducer regimens than those using noninducer regimens throughout (p=.02). The free LNG index was lower (ranging from 39% to 45.6%) in WWE using inducer regimens than those using noninducer regimens (p<.0001) from 21 days to 6 months of LNG-IUD use. Total LNG concentration and endometrial thickness were similar between WWE using inducer and noninducer regimens (Supplemental Fig. 1).

The median number of B/S days in each 30-day period decreased 56%, 69% and 50% from month 1 to month 6 of LNG-IUD use. In first month of LNG-IUD use, the median [interquartile range (IQR)] number of B/S days was 16 (13–23), with 6.5 days (4–8.5) of bleeding only. In month 6, the median number of B/S days was 7 (2.5–10), with 2 days (0.5–4) of bleeding only. Results were similar by AED group (supplemental Fig. 2).

Analysis by reference period showed that most WWE experienced normal bleeding (i.e., from 3 to 5 B/S episodes in each RP) in both RPs. The percentage of WWE with frequent and prolonged bleeding decreased from RP1 to RP2 (Table 3).

4. Discussion

Our findings suggest that WWE who initiated the LNG-IUD experienced stable total LNG concentration and gradually decreasing endometrial thickness and bleeding over the first 6 months of use.

The total LNG concentrations in our study fell in the range expected at 6 months according to product monograph (25th–75th percentiles: 151–264 pg/mL) [7]. However, mean/median total LNG concentrations were lower than those reported in most studies of LNG-IUD users without epilepsy [7,8,26–28]. Comparing our results with studies of women

Table 2
Levonorgestrel exposure and endometrial thickness in WWE at different times after LNG-IUD placement

	Baseline $n = 20$	21 days $n = 20$	3 months $n = 20$	6 months $n = 20$
Total LNG (pg/ml)				
Median (IQR)	0	157 (137–223)	168 (134–182)	157 (116–179)
Mean (SD)	0	181 (76)	161 (54)	153 (49)
Free LNG index (pg/ml)				
Median (IQR)	0	1.3 (1.0–1.5)	1.5 (1.1–1.7)	1.3 (1.0–1.6)
Mean (SD)	0	1.3 (0.4)	1.4 (0.4)	1.3 (0.3)
SHBG (nmol/L)				
Median (IQR)	41.9 (32.8–55.2)	43. 6 (29.9–53.6)	36.1 (25.7–46)	36.2 (28–52.4)
Mean (SD)	44.6 (16.7)	46.6 (20.5)	37.5 (13.6)	40.2 (17.1)
ET (mm)[a]				
Median (IQR)	3.3 (1.7–6.6)	5.9 (4.6–7.5)	4.5 (3.7–5.6)	3.3 (2.8–4.9)
Mean (SD)	3.8 (2.5)	6 (2)*	4.7 (1.4)	4.1 (1.8)*

All statistical analyses were performed using linear mixed-effects model adjusted for multiplicity by Bonferroni correction.
ET, endometrial thickness.
[a] Except for baseline, ET was measured on day 21 of each month.
* p=.02 (between 21 days and 6 months.

Table 3
Bleeding patterns associated with LNG-IUD device use in WWE

Classification of the bleeding patterns	RP 1 Participants, *n* (%)	RP2 Participants, *n* (%)
Frequency		
Amenorrhea	-	-
Infrequent	-	4 (20)
Normal	16 (80)	14 (70)
Frequent	4 (20)	2 (10)
Duration		
Prolonged	10 (50)	3 (15)
Not prolonged	10 (50)	17 (85)

without epilepsy requires cautious interpretation; those studies excluded AED users, measured plasma LNG instead of serum [26,27], used liquid chromatography–tandem mass spectrometry (LCMS) instead of RIA [26], assessed different time points of LNG measurement [8,26,27] and studied a higher dose LNG-IUD [27].

LNG-IUD use causes gradual changes in SHBG levels [8]. We observed a 13% decrease in SHBG among WWE in our study, not expected to be clinically meaningful [8].

LNG binds with high affinity to SHBG, and less than 2% of the total LNG concentration is unbound in the circulation [8,29]. Therefore, SHBG fluctuations can change free LNG concentrations. We observed higher levels of SHBG in WWE using enzyme-inducing AEDs compared to WWE using non-enzyme-inducing AEDs, which is expected and previously described [30]. Accordingly, high levels of SHBG found in enzyme-inducing AEDs users were associated with a lower free LNG index (39%–45.6% lower). The clinical relevance of this finding requires further investigation.

Methods to evaluate free hormones have a degree of inaccuracy; many factors influence hormone transit in vivo and measurement in vitro. Ultrafiltration and equilibrium dialysis, the reference techniques for direct and indirect measurement of free hormones, are expensive and technically challenging [31–33]. The choice between direct or indirect assessment depends on the concentration of the free hormone tested; very low concentration of some free hormones in the serum/plasma makes the direct approach unfeasible even for sensitive LCMS assays. As an easier and less costly alternative, some proxies for indirect assessment of free hormones (e.g., algorithms based on law of mass action, equations derived from computer modeling and free androgen index) provide a fair correlation to the reference methods in most situations [31–34]. Similar to free testosterone [32,34], unbound LNG is usually measured indirectly using the free LNG index, equations derived from computer modeling, and the mass-action equation using LNG binding affinities to SHBG and albumin [8,16,17,35]. To the best of our knowledge, there is no study measuring free serum/plasma LNG concentrations from LNG-IUD users by ultrafiltration and equilibrium dialysis.

Bleeding-related problems cause LNG-IUD discontinuation [5,36]. Accurate counseling about expected bleeding changes is pivotal to continuation and satisfaction [37,38]. Bleeding and spotting days decreased 56% over 6 months of LNG-IUD use in WWE, similar to women without epilepsy [36,39–43], and bleeding patterns were also similar to healthy peers [37,44,45]. We lacked adequate participants to conduct robust comparisons of bleeding outcomes by AED inducer status.

Study strengths include complete follow-up and ascertainment of outcome measurements in a special population. This pilot study had limitations. The small sample size limited power to detect differences based on AED inducer status, and few WWE using inducer AEDs were included. This imbalance reflects local clinical practice; enzyme-inducing medications are prescribed less than non-enzyme-inducing AEDs. Recruitment proved challenging [11]; a larger study could explore differences related to AED inducer status if adequate sites were available to enroll participants reflecting more varied AED prescribing practices. Free LNG index is an acceptable proxy for unbound LNG [16,17]; however, reference techniques of ultrafiltration and equilibrium dialysis should confirm our findings. To date, we could not identify a study assessing agreement of the reference techniques with proxies to estimate unbound LNG. We did not measure endometrial LNG levels and ovarian steroid hormones (i.e., estradiol and progesterone), which could affect bleeding and vary by co-administered AEDs. Our study could not evaluate long-term bleeding patterns.

In conclusion, WWE treated with AEDs experienced stable serum LNG concentration and gradually decreasing endometrial thickness and bleeding over the first 6 months of LNG-IUD use, similar to their peers without epilepsy.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.contraception.2018.11.018.

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