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Ulipristal Acetate for Unscheduled Bleeding in Etonogestrel Implant Users: A Randomized Controlled Trial

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Abstract

OBJECTIVE—To evaluate if ulipristal acetate reduces the number of bleeding days in etonogestrel implant users in a 30-day period as compared to placebo.

METHODS—We performed a single-center, randomized, double-blind, placebo-controlled trial. Eligible participants were women aged 18–45 years with an etonogestrel implant in place for >90 days and <3 years who complained of greater than 1 bleeding episode in a 24-day period. Enrolled participants were randomized to receive 15mg of ulipristal acetate compared with an identical-appearing placebo daily for 7 days. Participants completed daily bleeding diaries using automated text messaging to evaluate if ulipristal acetate reduces the number of bleeding days as compared to placebo. Secondary outcomes included participant satisfaction with bleeding and effect of ulipristal acetate on ovulation status. A sample size of 52 per group (n=104) was planned, calculated with an effect size of a 30% reduction in bleeding days, standard deviation of 10 days, and drop out of 15%. Our study was terminated early (n=65) due to an FDA hold, but power was sufficient for analysis. Impact of ulipristal acetate on ovulatory potential was evaluated in a subset with weekly serum progesterone.

RESULTS—From May 2017 to January 2018, 65 women were allocated to receive 15mg ulipristal acetate (n=32) or placebo (n=33) daily for 7 days. Demographic characteristics were similar between groups. Women randomized to ulipristal acetate reported 5 fewer days of bleeding over a 30-day reference period after treatment (p=0.002). At the conclusion of the 30-day follow-up period, women in the ulipristal acetate group were more satisfied with their bleeding profile than the placebo group (87.5% vs 60%, respectively; p<0.001). Serum progesterone levels were non-ovulatory in a subset of each group (placebo group range: <0.2 to 1.3 ng/mL; ulipristal acetate group range: <0.2 to 4.4 ng/mL).

CONCLUSION—Ulipristal acetate is well-tolerated and reduced the number of bleeding days in etonogestrel implant users in our study.

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Dr. McNicholas receives research support from Merck and serves on the Merck Global Advisory Board for Contraception. Dr. Madden serves on a scientific advisory board for Bayer Healthcare Pharmaceuticals and on a data safety monitoring board for phase 4 safety studies of Bayer contraceptive products. The other authors did not report any potential conflicts of interest.

CLINICAL TRIAL REGISTRATION—ClinicalTrials.gov, NCT03118297.**INTRODUCTION**

The etiology of bleeding secondary to progestin-only contraception, such as the etonogestrel implant, is poorly understood. One leading theory is that sustained exposure to a progestin can lead to endometrial angiogenesis disruption, resulting in the development of a dense venous network that is fragile and prone to bleeding.¹ In a recent study evaluating reasons for discontinuation of a contraceptive method within 6 months of initiation, unscheduled bleeding was reported in 53% of women using the etonogestrel implant.² Treatment of unscheduled bleeding may increase implant acceptability and improve continuation rates. Pharmacologic therapies such as non-steroidal anti-inflammatories and estrogen have shown mixed results and may be contraindicated due to medical comorbidities.^{3,4}

Ulipristal acetate, a selective progesterone receptor modulator, is marketed for emergency contraception in the United States (US). Outside the US, it is available for treatment of abnormal uterine bleeding associated with uterine leiomyoma. Uterine bleeding is reduced or eliminated via antiproliferative effects due to mixed agonist and antagonist effects of ulipristal acetate within the endometrial and myometrial tissue.^{5,6,7,8,9} ulipristal acetate may also displace local progestin within the uterus to counteract bleeding secondary to the above-mentioned creation of a dense, fragile venous network.

The primary objective of this study was to evaluate the effectiveness of ulipristal acetate in decreasing bleeding days due to the etonogestrel implant over a 30-day period as compared to placebo. We hypothesized that ulipristal acetate would reduce total days of unscheduled bleeding. For our secondary outcomes, we also hypothesized that ulipristal acetate would increase satisfaction with bleeding and the implant, and not effect ovulatory status.

MATERIALS AND METHODS

We performed a randomized, double-blinded, placebo-controlled trial at Washington University School of Medicine in St. Louis, MO from May 2017 to January 2018. This study was approved by the Washington University School of Medicine Human Research Protection Office (February 8, 2017). Prior to initiation of the trial, a Food and Drug Administration Investigational New Drug application (FDA IND #134150) for ulipristal acetate was approved and the trial was registered at clinicaltrials.gov (NCT03118297). We used CONSORT guidelines in the planning of this study.¹⁰

We used poster advertisements and provider referrals from the St. Louis area to recruit English speaking women aged 18–45 years using the etonogestrel 68-mg subdermal implant (Nexplanon™, Merck, Kenilworth, NJ, USA). Women must have had their implant placed >90 days and <3 years prior to enrollment and report dissatisfaction with their bleeding pattern of greater than 1 bleeding episode in the previous 24-day period. Previous studies investigating therapies for unscheduled bleeding have used this definition.¹¹ Women must have been willing to complete a 30-day bleeding diary and have the ability to do so via text message. Finally, as ovulation suppression could theoretically be affected by addition of ulipristal acetate, participants were asked to either abstain from intercourse or use condoms

during the study period, which were provided at no cost. Participants were excluded if they reported a contraindication to ulipristal acetate (i.e. breastfeeding, use of CYP3A4 inducer such as carbamazepine and topiramate, use of oral glucocorticoids for uncontrolled severe asthma).

Following informed consent, eligible participants underwent a staff administered baseline survey in which demographic information, medical history, length of etonogestrel implant use, bleeding history in the 30 days prior to enrollment, and current level of satisfaction with bleeding pattern were collected. Current satisfaction with and intent to discontinue the etonogestrel implant due to unscheduled bleeding were assessed.

Participants received a pill bottle containing study drug that was created and dispensed by the Investigational Drug Pharmacy at Barnes-Jewish Hospital Washington University in St. Louis containing either seven 15mg ulipristal acetate capsules or 7 identical-appearing placebo capsules according to the randomization scheme. ulipristal acetate tablets in a 30mg dose were purchased from a manufacturer and delivered directly to the pharmacy. Ulipristal acetate tablets were cut in half, weighed, and over-encapsulated with gelatin capsules. Placebo capsules were made to look identical to ulipristal acetate capsules. Pill bottles were labeled by subject identification number and participant name.

Creation of the randomization scheme was performed by the study statistician in a 1:1 fashion with block sizes of 8 using a computer-generated random allocation rule. Once consent was obtained, a copy of the consent as well as a prescription for study medication was sent to the research pharmacy. The study medication was delivered by the pharmacist to the site of study enrollment. The pharmacy and study statistician were the only individuals with access to the randomization scheme. Unblinding occurred only after completion of all data collection.

Participants took their first dose of medication prior to leaving their enrollment visit and then daily thereafter for a total of 7 days. Prior to medication administration, a verification text message (via a third-party service, Twilio, through REDCap, Research Electronic Data Capture¹²) was sent to the participant to verify that she could receive text messages. Condoms and the remainder of the study medication were given to the participant at the end of her enrollment visit.

Participants completed daily bleeding diaries via automated text message to evaluate the effectiveness of ulipristal acetate in reducing bleeding days due to the etonogestrel implant over a 30-day period as compared to placebo. For 30 days, participants used single digits to code if they had taken their medication (for first week of study period only), if they had bleeding, and if so, how much based on the Pictorial Blood Assessment Chart. If the initial text message was not answered, it was automatically sent up to 2 subsequent times that day. Diaries were monitored every 72 hours to assess for completeness by the study team. Participants with missing data were contacted by phone to complete the missing logs and assess desire to continue the study. A subject was considered lost to follow-up after 2 weeks of no contact.

Participants were called weekly for 4 weeks to complete a follow-up survey. This survey assessed ease of medication use (first week only), medication satisfaction, any side effects experienced, and if participants used condoms if sexually active. Twenty participants from both groups volunteered to take part in a study subset assessing ovulation status. These participants had weekly in-person follow up visits where the same survey was administered in addition to a blood draw testing serum progesterone levels. Blood was drawn by a medical assistant or nurse and immediately sent to the Core Laboratory at Washington University in St. Louis for analysis. Potential for ovulation was defined as a progesterone level above 5ng/mL.¹³ All participants were called at the end of the study to complete an exit survey assessing bleeding pattern satisfaction and if their bleeding was bothersome enough to have the etonogestrel implant removed. Participants were compensated with gift cards for their time and effort.

Participant characteristics are presented as means, standard deviations, frequencies, and percentages. Length of implant use and number of bleeding days were evaluated using medians and interquartile ranges (IQR). We used a chi-square test for categorical data and Student's t-test or Mann-Whitney U test for continuous variables, where appropriate (Table 1). Number of bleeding days during the study calculated from daily bleeding diaries were compared using a Mann-Whitney U test. Participant satisfaction with bleeding pattern, side effects experienced, medication satisfaction, and desire to continue using the contraceptive implant are presented with frequencies and percentages. Chi-square test and Fisher's exact test were used, where appropriate. All analyses were performed using SAS (Version 9.4, SAS Institute Inc., Cary, NC). A p-value <0.05 was considered statistically significant.

We calculated that 104 women (52 in each group) would be required to detect a 30% reduction in number of bleeding days with an alpha of 0.05 and 80% power. Previous literature demonstrates that women with the contraceptive implant have an average of 20 bleeding days per month,¹⁴ therefore, our effect size was a decrease by 6 days, which we felt to be a clinically relevant estimate. As there was no literature regarding the use of ulipristal acetate for bleeding secondary to the etonogestrel implant, we extrapolated from literature regarding other therapies used for unscheduled bleeding secondary to the etonogestrel implant to define our standard deviation of 10. We assumed a 15% loss to follow-up rate. In December 2017, we were notified by the FDA that a hold was being placed on all research evaluating the use of ulipristal acetate. We had previously performed an interim analysis halfway through enrollment that showed a pooled standard deviation of 7, which was lower than previously accounted for. Communication with the FDA indicated a likely lengthy delay. The Data Safety and Monitoring Board was then consulted and given the findings of the interim analysis, the decision was made to perform a second interim analysis when the last currently enrolled participant completed their 30-day follow-up window. The pooled standard deviation was again found to be 7. Additionally, we also noted a much smaller loss to follow-up rate (3%) than we previously planned for. Using the observed standard deviation of 7, loss to follow-up rate of 3%, and the completed enrolled sample size of 65, we determined the study had achieved 90% power to assess for a 30% reduction in bleeding days and thus, enrollment was stopped.

RESULTS

We assessed a total of 336 women for eligibility. Sixty-five women were ultimately randomized with 33 allocated to the placebo group and 32 to the ulipristal acetate group. Two participants in the placebo group were lost to follow-up (no longer answered text messages or telephone calls), leaving 63 participants for analysis, 31 in the placebo group and 32 in the ulipristal acetate group (Figure 1). All participants reported taking all 7 pills as dispensed. There were 3 participants missing a total of 9 bleeding diaries from the 30-day period for 0.48% missing data. Due to the extremely low rate of loss to follow-up, imputation of missing values was not performed. Table 1 compares baseline demographic characteristics of the analysis sample. Groups were similar in all aspects, including length of implant use (median use in months, placebo 9.2, ulipristal acetate 10.9, $p=0.84$) and reported number of bleeding days the month prior to enrollment (median days, placebo 20.0, ulipristal acetate 20.5, $p=0.79$).

At the end of the 30-day follow-up period, the median number of bleeding days was 12.0 (IQR 6–21) in the placebo group and 7.0 (IQR 4.5–11) in the ulipristal acetate group ($p=0.002$). Three women in the placebo group (9.7%) and eleven women in the ulipristal acetate group (34.4%) had bleeding cessation by day 10 ($p=0.03$). Figure 2 presents participant satisfaction with bleeding pattern at baseline and at the end of the study. At baseline, both groups had similar satisfaction levels. Women in the ulipristal acetate group were more likely to be satisfied with their bleeding pattern at the end of the study; 71.9% of women in the ulipristal acetate group were “very happy” with their bleeding as opposed to 26.7% in the placebo group ($p<0.001$). While 27/32 women in the ulipristal acetate group at study initiation reported they were “not at all happy” or “somewhat unhappy” with their bleeding at baseline, there were no participants reporting these levels of dissatisfaction at the conclusion of the study. At baseline, groups were similar in their desire to have their implant removed due to bothersome bleeding, with the majority stating they would desire removal (placebo group 63.3%, ulipristal acetate group 67.7%, $p=0.72$). At the end of the study, more women in the ulipristal acetate group desired to keep their implant than in the placebo group (89.7% vs. 63.3%, $p=0.03$).

There were few side effects reported during the treatment period, including headache (19.4% in placebo group, 9.4% in ulipristal acetate group) and nausea and vomiting (9.7% in placebo group, 3.1% in ulipristal acetate group). Groups were similar in side effects experienced, with the majority experiencing no side effects (placebo group 74.2%, ulipristal acetate group 81.3%, $p=0.5$). We did not encounter any serious adverse events. All participants from both groups felt their medication was easy to use. One-hundred percent of ulipristal acetate users stated they would use the medication again for bleeding, which was significantly different than placebo users (66.7%; $p=0.001$).

While not powered to detect a difference for ovulatory status, no participants in either group (subset of 20 per group) were noted to have ovulatory progesterone levels (placebo group range: <0.2 to 1.3 ng/mL; ulipristal acetate group range: <0.2 to 4.4 ng/mL).

DISCUSSION

We found that administration of ulipristal acetate was associated with a reduction in the number of bleeding days due to the etonogestrel implant over a 30-day period as compared to placebo. Women who used ulipristal acetate had higher levels of satisfaction with their bleeding pattern at the end of the study period compared to placebo and would be more likely to continue the implant as their contraceptive method. Placebo users did become more satisfied with their bleeding and implant, which may be due to objective measuring of bleeding days as well as placebo effect. Ulipristal acetate users identified minimal side effects, found the medication easy to use, and would use the medication again, if necessary. Ovulatory progesterone levels were not noted, therefore etonogestrel implant efficacy was not felt to be altered, but more research is needed to confirm as we were not powered for this outcome.

Numerous studies have investigated therapies for the treatment of unscheduled bleeding with progestin-only contraceptive methods, however, none included the use of ulipristal acetate with the etonogestrel implant.^{3,4} The mechanism by which ulipristal acetate may reduce unscheduled bleeding associated with the etonogestrel implant is unclear, though it may be due to antiproliferative effects.⁵

Our study has limitations. First, no pilot data was available to determine the ideal dosing and duration for ulipristal acetate for bothersome bleeding in implant users. Our regimen was chosen based on feasibility; the currently available dose of ulipristal acetate in the United States is 30mg, allowing the pharmacy to easily cut the pill in half for a 15mg dose. We felt a 7-day regimen would be acceptable to women. We did not design this study with a run-in period, therefore number of bleeding days in the 30 days prior to enrollment was self-reported, which may be less accurate due to recall bias. We felt that a run-in period would have led to difficulties with recruitment and higher rates of loss to follow-up as many women who present with complaints of unscheduled bleeding want immediate treatment or implant removal. While we ultimately found a lower number of days in our placebo group than reported, it is possible that women unhappy with their bleeding may overestimate their number of bleeding days. It is important to note, however, that both groups reported the same amount of bleeding days initially. We did need to end our study early due to a FDA hold regarding liver toxicity in some women using Esmya (ulipristal acetate 5mg daily for 3 months for uterine leiomyoma) overseas. Since our study completion, the European Medicines Agency has determined that Esmya should not be used in women with known liver problems and that liver function tests should be followed before, during, and after use. Esmya is a much longer course of ulipristal acetate than we have proposed, but further research should likely adhere to these recommendations.¹⁵ Finally, we were not powered to detect an effect on ovulatory status, which was used as a proxy for etonogestrel implant efficacy. To detect such a small difference would likely require a sample size over 500. We are reassured, however, that no ovulatory progesterone levels were found in the subset of either treatment group.

Our study also has many strengths, which include being a randomized, double-blinded, placebo-controlled trial. Use of automated text messaging for daily bleeding diaries led to

low drop-out and missing data rates, leading to greater internal validity. Additionally, ulipristal acetate is a novel therapy for unscheduled bleeding associated with the etonogestrel implant. Unlike many other therapies used for unscheduled bleeding due to progestin-only contraception, ulipristal acetate has few contraindications and thus, could be used more widely. Finally, as we had very few exclusion criteria and participants were racially and economically diverse, we feel the results are generalizable to reproductive-aged women.

Our study demonstrates that in women with unscheduled bleeding due to the etonogestrel implant, ulipristal acetate use led to a greater decrease in bleeding days compared to placebo, as well as increased satisfaction with bleeding pattern and the etonogestrel implant. Increased satisfaction with the etonogestrel implant may lead to a decrease in discontinuation rates, and potentially a decrease in unintended pregnancy rates in this population. The only other study evaluating ulipristal acetate for progestin-mediated bleeding (50mg ulipristal acetate for 3 days beginning on days 21, 49, and 77 after levonorgestrel intrauterine device insertion) showed benefit in the short-term but not long-term.¹⁶ However, a different progestin was used in this study and therapy was given to prevent bleeding, not treat it. Further investigation of ulipristal acetate in different dosages and regimens, as well as for longer follow-up periods is warranted.

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Figure 1.
Flow diagram.

Figure 2.

Bleeding satisfaction. Ulipristal acetate compared with placebo at baseline (A) and week 4 (B). Fischer's exact test: $P=.39$ for baseline and $P<.001$ for week 4.

Table 1

Demographic Characteristics

Demographic	Placebo (N=31)		Ulipristal acetate (N=32)	
Age, mean $\pm$ SD	25.5	$\pm$ 6.3	26.4	$\pm$ 6.2
BMI, mean $\pm$ SD	27.8	$\pm$ 7.0	29.6	$\pm$ 8.2
Race, n (%)				
Black	21	(67.7)	20	(62.5)
White	7	(22.6)	7	(21.9)
Other or multiracial	3	(9.7)	5	(15.6)
Hispanic, n (%)				
Yes	2	(6.5)	0	(0.0)
No	29	(93.5)	32	(100.0)
Marital status, n (%)				
Never married	22	(71.0)	23	(71.9)
Not married but living with a partner	6	(19.3)	9	(28.1)
Married	3	(9.7)	0	(0.0)
Education, n (%)				
Less than high school	0	(0.0)	0	(0.0)
High school or GED	5	(16.1)	10	(31.2)
Some college	16	(51.6)	16	(50.0)
College and graduate degree	10	(32.3)	6	(18.8)
Parity, n (%)				
0	17	(54.8)	14	(43.7)
1	7	(22.6)	5	(15.6)
2	3	(9.7)	7	(21.9)
3+	4	(12.9)	6	(18.8)
Medical conditions, n (%)				
Fibroids	1	(3.2)	1	(3.1)
High blood pressure	0	(0.0)	3	(9.4)
Migraines with aura	6	(19.4)	2	(6.3)
Peptic ulcers	2	(6.5)	1	(3.1)
Duration of implant use in months, median (IQR)	9.2	(5.9 – 19.3)	10.9	(5.5 – 18.1)
Days of bleeding in 30 days prior to enrollment, median (IQR)	20.0	(14.0 – 28.0)	20.5	(12.5 – 29.5)

BMI, Body Mass Index; IQR, Interquartile Range