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ORIGINAL RESEARCH ARTICLE

Combined oral contraceptive treatment for bleeding complaints with the etonogestrel contraceptive implant: a randomised controlled trial

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ABSTRACT

Objective: Estimate symptom improvement rate of women with bleeding complaints using the etonogestrel contraceptive implant when started on continuous combined oral contraceptives (COC).

Methods: We conducted a double-blinded randomised controlled trial of women reporting troublesome bleeding related to their etonogestrel contraceptive implant and desiring intervention. Participants received continuous COCs or placebo for four weeks to evaluate self-reported bleeding improvement at four weeks. Participants could continue study treatment or prescribed COCs for another eight weeks if desired. We planned to enroll 130 participants between two sites (80% power to detect a 20% effect size at a 0.05 significance level, with 10% loss to follow up).

Results: We closed the study after enrolling 26 participants due to recruitment futility. All women on COCs and 75% of placebo users reported bleeding improvement at four weeks ($p = 0.09$), with 92% and 42%, respectively, reporting significant improvement ($p = 0.03$). The median number of days until bleeding stopped for at least four days in COC and placebo users was 1 day (range 1–9) and 4.5 days (range 1–28), respectively ($p = 0.63$). Eight (75%) COC and five (42%) placebo users opted to continue study treatment ($p = 0.41$). Despite bleeding improvement, women who desired implant removal at enrollment were more likely to re-request removal than those who initially considered other interventions (3 of 5 [60%] vs 1 of 17 [6%], $p = 0.03$).

Conclusion: Although women who have troublesome bleeding while using the contraceptive implant may experience improvement with no treatment over 4 weeks, women using COCs are more likely to report significant improvement.

Clinicaltrials.gov registration number: NCT01963403.

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Contraception; implant; etonogestrel; bleeding; combined oral contraceptive

Introduction

The etonogestrel (ENG) implant is a highly effective long-acting reversible contraceptive, currently approved for 3 years of use with a relatively quick return of fertility upon its removal. Menstrual irregularities are common with long-acting progestin products and can often be the primary factor for discontinuation or removal.

Discontinuation rates due to bleeding irregularities have been reported to be 13–23%.^[1–3] However, few studies have attempted to evaluate effective treatments for bleeding irregularities in women using the ENG implant.^[4–6] A recently completed study performed during the time course of this study randomised 32 women with 7 or more days of 'bothersome' bleeding to 14 days of a COC containing EE 30 mcg and levonorgestrel 150 mcg or placebo.^[7] Although, the COC quickly decreased the bleeding, the bleeding returned within days of treatment cessation.

We evaluated COC treatment for at least four weeks but up to 12 weeks in women complaining of significant bleeding problems with the ENG contraceptive implant. Our primary goal of evaluating if bleeding improved with treatment was measured by subjective participant response of whether she felt her bleeding improved and desired continued use of her implant.

Methods

We enrolled women in a double-blind, placebo-controlled randomised multicentre trial at the University of California, Davis (Sacramento, CA) and Washington University in St. Louis (St. Louis, MO). The institutional review boards at each institution approved the study. We registered the study with Clinicaltrials.gov, identifier number NCT01963403. All subjects signed written informed consent before starting any study procedures.

We recruited women 14 years and older who presented for care to our offices or a referring provider requesting intervention (treatment or implant removal) for complaints of significant bleeding irregularity or heavy flow. They were not required to be bleeding on the day of enrollment. We excluded women with one or more conditions considered Category 3 (risks outweigh benefits) or Category 4 (unacceptable health risk) for estrogen-containing contraceptives by the Centers for Disease Control and Prevention (CDC) United States Medical Eligibility Criteria,^[8] who had previously received prescription treatment for bleeding while using the implant, had orthostatic vital signs, or who had other potential organic causes for the bleeding complaints such as uterine fibroid or cervical polyp.

We randomised eligible subjects to receive a monophasic COC (EE 30 mcg/levonorgestrel 150 mcg) or placebo for

28 days. A statistician unrelated to the study protocol provided a 1:1 randomisation schema to the pharmacy at each institution. The pharmacist at each site placed one oral contraceptive or placebo tablet in a gelatin capsule and then filled each treatment bottle with 28 capsules. We elected 28 days of initial treatment to mimic the number of days in most commercially available COC packages. We provided the subject with the next sequentially numbered vial for the first cycle and a daily diary to indicate drug use and bleeding flow.

Participants returned for a one-month follow-up visit during the last week of study drug use (study days 22–28). The subject informed the study staff if she felt the treatment improved her bleeding and if she was interested in continuing use of her ENG implant. The subject could then choose any of the following: (1) continue her assigned treatment for up to two more cycles; (2) no further treatment and continue with ENG implant; (3) open-label (non-study) COC treatment; or (4) ENG implant removal. We continued to follow subjects until either ENG implant removal or up to two additional months. We asked all women still using the ENG implant to attend a final 3-month visit during the time equivalent to the last week of two more COC cycles (study days 78–84). We chose three months of treatment as a clinically relevant time point since women who start new hormonal contraception often have transient side effects that usually resolve by 12 weeks.^[9] Subjects could select the same options offered at the previous visit with the exception that they could not continue their assigned study treatment. We collected adverse events at each study visit.

We hypothesised that continuous use of a monophasic combined oral contraceptive would significantly improve bleeding patterns for ENG implant users with significant bleeding irregularity or heavy flow. Women reported overall changes in bleeding using a 5-point Likert scale (improved significantly, improved slightly, no change, worsened slightly, worsened significantly). We defined the time to bleeding cessation as the number of days from treatment initiation to subject report of four consecutive days without bleeding. If women were not bleeding on day of treatment initiation, that day was considered the first of the four days. We also hypothesised that amongst women who expressed the desire for implant removal at enrollment, ultimate continuation with the method would be higher in those randomised to the treatment arm.

We estimated a sample size based on a primary outcome of improved bleeding during the first cycle of study treatment. Subjective improved bleeding was measured by participants' self-determination that her bleeding improved. We chose subjective outcomes as we felt this would be the most clinically relevant outcome and best reflect real-world patient reactions to bleeding while using the implant. Assuming that 90% of women would improve with treatment and 70% would have improvement with placebo, a sample of 118 women would provide 80% power to detect this 20% effect size at a 0.05 significance level. We increased the sample to 130 to account for potential lost to follow-up. We planned to enroll 26 subjects at the University of California, Davis and 104 subjects at Washington University due to the latter site's prior success with implant study recruitment.^[10]

We used Fisher's exact testing and Chi-square analysis as appropriate. We analysed data using SAS 9.3 (SAS Institute Inc., Cary, NC).

Results

From November 2013 to June 2015, we enrolled 26 subjects (21 subjects at the University of California, Davis and five at Washington University) and discontinued the study early due to recruitment futility. Participants ranged in age from 17 to 34 years, with three of the 26 subjects aged 21 years or less (Table 1). In general, subjects were white or black, non-Hispanic, single and educated. Women in the placebo group had used the implant for a shorter duration than women in the COC group (median 109 days [41–518 days] vs 343 days [25–764 days], $p = 0.15$).

Participants reported that their bleeding patterns before ENG implant placement as primarily regular and predictable, lasting six days or less with moderate flow and little or no unscheduled bleeding (data not shown). Bleeding patterns of enrollees after initiating the contraceptive implant always included irregular bleeding (100%) but also heavy (62%) and intermenstrual (58%) bleeding. Women most commonly described bleeding with the contraceptive implant as unpredictable, moderate in flow, frequent and long in duration (seven or more days) (Table 2).

Flow of study participants is shown in Figure 1. Twelve of the 13 women in each group returned for follow-up after one cycle of treatment. All 12 COC users and 8 (75%) of 12 placebo users noted improvement in bleeding ($p = 0.09$) (Figure 2). More women noted 'significant' improvement with COC use ($n = 11$ [92%]) than placebo ($n = 5$ [42%]), $p = 0.03$. No women in the COC group complained of worse bleeding, compared to two (17%) placebo users ($p = 0.48$). All 12 COC users and 8 (75%) placebo users stopped bleeding during the first four weeks of treatment. COC users and placebo users who stopped bleeding did so after a median of 1 day (range 1–9) and 4.5 days (range 1–28), respectively ($p = 0.63$).

Eight (75%) women in the COC group and 5 (42%) in the placebo group opted to continue the study treatment ($p = 0.41$). Four women in each group chose to begin open-label COC treatment. Only one subject (placebo group) opted for implant removal; of note, she had entered the trial desiring implant removal and she continued to have bothersome bleeding throughout the study.

All 12 women in the COC group and nine of 12 women in the placebo group returned for the three-month follow-up visit. Overall, 12 of 16 (81%) women who used COCs for two or more months during the course of the study noted improvement in bleeding patterns; all five of the women who continued placebo also improved ($p = 0.54$). Interestingly, three of the 15 women who used COCs during the course of the study reported no bleeding improvement at three months.

Nearly half of all subjects at the 3-month visit (9 of 21) still noted some unscheduled bleeding. Unscheduled bleeding occurred in 6 of 16 (38%) women using COCs and 3 of 5 (60%) women not using any treatment ($p = 0.61$).

Over the course of the study, four women opted for implant removal, with three of the four requesting removal at the end of the trial. Two had used a COC at some time

Table 1. Characteristics of women enrolled in a randomised trial evaluating combined oral contraceptive and placebo for treatment of bleeding complaints with an etonogestrel contraceptive implant.

	Total N = 26	COC n = 13	Placebo n = 13
Age (years)	25.6 ± 4.3	25.4 ± 3.8	25.8 ± 5.0
Race			
White	10 (39%)	5 (38%)	5 (38%)
Black	7 (27%)	4 (31%)	3 (23%)
Asian	3 (12%)	1 (8%)	2 (15%)
Native Hawaiian/Pacific Islander	2 (8%)	1 (8%)	1 (8%)
Biracial	2 (8%)	1 (8%)	1 (8%)
Other	1 (4%)	1 (8%)	0
Missing information	1 (4%)	0	1 (8%)
Hispanic ethnicity ^a	0	0	0
Weight			
BMI (median, range)	24.1 (18.9, 43.9)	26.5 (18.9, 38.9)	23.1 (21.0, 43.9)
Obese	6 (23%)	4 (31%)	2 (15%)
Gravidity			
0	9 (35%)	5 (38%)	4 (31%)
1	9 (35%)	4 (31%)	5 (38%)
2 or more	3 (12%)	1 (8%)	2 (15%)
3 or more	3 (12%)	1 (8%)	2 (15%)
Missing information	2 (8%)	2 (15%)	0
Parity			
0	17 (65%)	8 (62%)	9 (69%)
1	4 (15%)	1 (8%)	3 (23%)
2 or more	3 (12%)	2 (15%)	1 (8%)
Missing information	2 (8%)	2 (15%)	0
Relationship			
Single	9 (35%)	4 (31%)	5 (38%)
Partner	16 (62%)	9 (69%)	7 (54%)
Missing information	1 (4%)	0	1 (8%)
Education			
High school or less	5 (19%)	3 (23%)	2 (15%)
Some college	10 (38%)	5 (38%)	5 (38%)
College degree	11 (42%)	5 (38%)	6 (46%)
Duration of implant use (median, range) ^b	144.5 (25, 764)	343 (25, 764)	109 (41, 518)
Primary reason for implant			
Contraception	23 (88%)	11 (85%)	12 (92%)
Bleeding problem	2 (8%)	1 (8%)	1 (8%)
Dysmenorrhea	1 (4%)	1 (8%)	0
Intervention requested before enrollment			
Implant removal	5 (19%)	2 (15%)	3 (23%)
Hormonal treatment	10 (38%)	6 (46%)	4 (31%)
'Some treatment'	11 (43%)	5 (38%)	6 (46%)

^a1 missing response.^bp = 0.15

Data are presented as n (%) or median (range) unless otherwise indicated.

COC: combined oral contraceptive.

Table 2. Bleeding patterns at study entry in women with bleeding complaints while using etonogestrel contraceptive implant.

	Total N = 26	COC n = 13	Placebo n = 13
Flow			
Spotting	0	0	0
Light	8 (31%)	4 (31%)	4 (31%)
Moderate	12 (46%)	5 (38%)	7 (54%)
Heavy	6 (23%)	4 (31%)	2 (15%)
Frequency			
<21 days	17 (65%)	8 (62%)	9 (69%)
21–35 days	2 (8%)	1 (8%)	1 (8%)
>35 days	2 (8%)	1 (8%)	1 (8%)
No 'cycles'	5 (8%)	3 (23%)	2 (15%)
Duration			
<5 days	6 (23%)	3 (23%)	3 (23%)
5–6 days	2 (8%)	0	2 (15%)
>6 days	18 (69%)	10 (77%)	8 (62%)
Predictability			
50% of the time	3 (12%)	0	3 (23%)
Most of the time	0	0	0
Every time	0	0	0
Unpredictable	23 (88%)	13 (100%)	10 (77%)

Women were randomised to combined oral contraceptive (COC) or placebo. Data are presented as n (%).

more likely to request removal later during the study (3 of 5 [60%] vs 1 of 17 [6%], $p = 0.03$).

Adverse events in the first four weeks that affected more than one participant included headache ($n = 10$), nausea or vomiting ($n = 3$), cramping ($n = 3$) and breast tenderness ($n = 4$). We found no differences in these events or in median weight changes over the first four weeks between groups.

Discussion

Findings and interpretation

Although this study did not achieve its projected sample, we believe it is important to learn from both the limited findings and the recruitment difficulties we encountered. Because we enrolled only 20% of the estimated sample, the study population is too small for substantial subgroup and regression analyses.

Women randomised to a COC more frequently reported that bleeding was significantly improved after one cycle of use than did women treated with placebo. Most (13 of 16, 81%) women who used a COC continuously for 2 or 3 months during the study noted improvement in bleeding

during the trial, and two (one placebo group, one COC group) elected removal after three months despite reporting significant bleeding improvement. The women who expressed desire for implant removal at enrollment were

Figure 1. Study flow of participants. COC: combined oral contraceptive.

Figure 2. Bleeding improvement with 4 weeks of combined oral contraceptive (COC) or placebo use in women with bleeding complaints while using etonogestrel contraceptive implant.

complaints, even though some still experienced periods of unscheduled bleeding.

Differences in results and conclusions in relation to other studies

Our findings are important as we assess the recently published study from Guiahi et al.[7] These investigators also performed a double-blind randomised controlled trial that included 64 women enrolled over 13 months complaining of 'bothersome' bleeding. Subjects received the same COC used in our study or placebo for 14 days. The authors reported interruption of bleeding by day 14 in 87.5% of COC users and 37.5% of placebo users ($p < 0.01$). However, bleeding restarted for most women shortly after discontinuing COCs, averaging 5.5 days, with 12 of 14 (85.7%) experiencing bleeding within 10 days of the end of treatment.

Taken together, our current study and that of Guiahi et al. [7] demonstrate two important points. First, use of a COC can help women feel that their bleeding is improved. In our study, all COC users stopped bleeding by treatment day 10. However, because we had no subjects in our study who used a COC and then stopped using it while under the protocol, we have no information on bleeding patterns or satisfaction after COC discontinuation. We do not know if a longer course of COCs results in a better post-treatment bleeding pattern as compared to a short course of 14 days.

Secondly, both studies encountered significant recruitment difficulties.[7] Guiahi et al. initially enrolled subjects from their clinics with poor success. They added radio advertising which enabled the investigators to enroll 32 women over 13 months as planned (Guiahi, personal communication). However, this recruitment tactic does not reflect clinical practice since we do not air radio

advertisements for our patients; in clinical practice, we would simply tell them to contact our office if the bleeding is a problem. The futility in recruitment in our current study is potentially related to the fact that once women actually present with bleeding, they may prefer implant removal over medical treatment. In fact, most of the women in our study who initially wanted removal ultimately had the device removed, even if their bleeding patterns had improved with treatment. Anticipatory counselling may play an important role in this reaction, and we could not control for patient counselling at the time of insertion in our study. Consequently, if women present to the office with significant bleeding complaints, it may be too late to prevent discontinuation with a medical treatment.

Strengths and weaknesses of the study

Because we obtained a detailed bleeding history at study entry, we are able to demonstrate the significant changes that can occur in women who have relatively regular menses prior to ENG implant use. Women enrolled in this study because they desired treatment for their bleeding. Thus, our participants may not represent all women who have bleeding issues with the ENG implant, but may more likely have extreme bleeding complaints that could lead to method discontinuation. Because we had no subjects in our study who used a COC and then stopped using it while under study protocol, we have no information on bleeding patterns or satisfaction after COC discontinuation. Of note, Guiahi et al.[7] reported another bleeding episode in 86% of women within 10 days of discontinuing COC therapy of problematic bleeding with ENG implant use. Additionally, similar to Guiahi et al.,[7] we encountered significant recruitment difficulties, enrolling only 20% of the estimated sample. This smaller sample size increases the risk of type-1 error in our primary outcome of bleeding improvement at one month.

Relevance of the findings: implications for clinicians and policy-makers

Overall, our role as clinicians is to help a woman choose the best contraceptive method for her and anticipate the potential side effects. For women choosing the implant, understanding the possibility of irregular bleeding and potential interventions are important to minimise early discontinuation.[1,2] Both our current study and that of Guiahi et al. [7] show that COC treatment can improve problematic bleeding. One proposed approach may be to encourage clinicians to be more pro-active than reactive. For women without contraindications to combined hormonal contraceptives, providing an advanced prescription for treatment to have at home in case of problematic bleeding may be an option to consider, rather than waiting for women to contact our office with complaints.

Unanswered questions and future research

Our study shows that women may experience improved bleeding without intervention, although those who receive COCs are more likely to report significant improvement. Further research on the use of advanced prescription for

treatment would help evaluate the effectiveness and patient satisfaction of such an approach. More information about bleeding patterns after treatment cessation would also aid counselling. Our study did not include women who had a contraindication to our study intervention. For these women, a selective estrogen or progesterone receptor modulator or a metalloproteinase inhibitor may be helpful. A prior study demonstrated that 25 mg mifepristone twice a day for one day followed by 100 mg doxycycline twice a day for five days is more effective than doxycycline, doxycycline with ethinyl estradiol and placebo for stopping a bleeding episode, though subsequent bleeding patterns did not differ between treatments.[6] However, the reasons for the significant recruitment difficulties that we encountered should also be explored as potential barriers to research on managing side effects of contraception.

Conclusion

Although women who have troublesome bleeding while using the contraceptive implant may experience improvement with no treatment over four weeks, women who use COCs are more likely to report significant improvement.

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Disclosure statement

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