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Original research article

Etonogestrel implant use in women primarily choosing a combined oral contraceptive pill: A proof-of-concept trial☆,☆☆,★

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ABSTRACT

Objective: We evaluated a novel concept of initiating the etonogestrel implant as a "back-up" method in women who desire using combined oral contraceptives (COC) but want to decrease their risk of unintended pregnancy with a more effective method.
Study Design: In this prospective cohort study, we planned to include 20 women as a proof-of-concept. We enrolled both new COC starters and continuing COC users and placed an etonogestrel implant. Participants completed daily bleeding diaries and attended follow-up visits at 1, 3, and 6 months. We assessed implant continuation through six months of study participation and side effects with dual hormonal contraceptive use.
Results: Between September and December 2016, we enrolled 10 new starters and 10 current COC users. All participants completed 1-month follow-up, and 18 (90%) subjects completed the 3- and 6-month follow-up assessments. Two current COC users had the implant removed for mood changes before 6 months. At the 6-month follow-up visit, 10 women were using both pills and implant, seven relied on the implant only, and one was using a COC only. Three new starters chose implant removal at end of study participation; one for weight gain and acne, another for mood changes, and one for decreased libido. No subjects discontinued the implant for bleeding complaints.
Conclusion: In this proof-of-concept study, women using COCs were willing to initiate the implant as a "back-up" method to improve pregnancy prevention. Most women continued the implant through 6 months and after completing study participation.
Implications: Initiating the etonogestrel implant as a "back-up" method may be an option for women who desire more effective pregnancy prevention while using combined oral contraceptive pills for its bleeding profile or non-contraceptive benefits.

1. Introduction

Oral contraceptives have consistently been the most commonly used contraceptive method among women in the United States for decades, with the most recent data estimating 25.3% of contraceptive users relying on pills [1]. In addition to taking pills for its contraceptive properties, over 50% of sexually active pill users choose pills for its non-contraceptive benefits, such as alleviating menstrual pain, regulating menstrual bleeding, acne, and endometriosis [2]. The 12-month probability of failure of pill use is higher at 7.2% compared with 0.4% with etonogestrel implants [3,4]. Yet, the continued high demand for oral contraceptives rather than the more effective implant implies that more women like or feel comfortable with a pill.

In women who want to use oral contraceptive pills but want to further decrease their risk of unintended pregnancy, one strategy is to offer the contraceptive implant as a "back-up" method to the pill, which would eliminate consequences of incorrect and inconsistent pill use while still using the preferred method. Dual use of combined oral contraceptives (COCs) and implant has been studied using COCs as a treatment for problematic bleeding in implant users [5,6]. These studies show that women using COCs experienced an improvement in bleeding for up to 3 months. Importantly, these studies demonstrated that women experienced few side effects while using the COCs and the implant at the same time. We performed this proof-of-concept study to evaluate etonogestrel implant continuation in women using COCs for contraception and side effects of combined COC and implant use.

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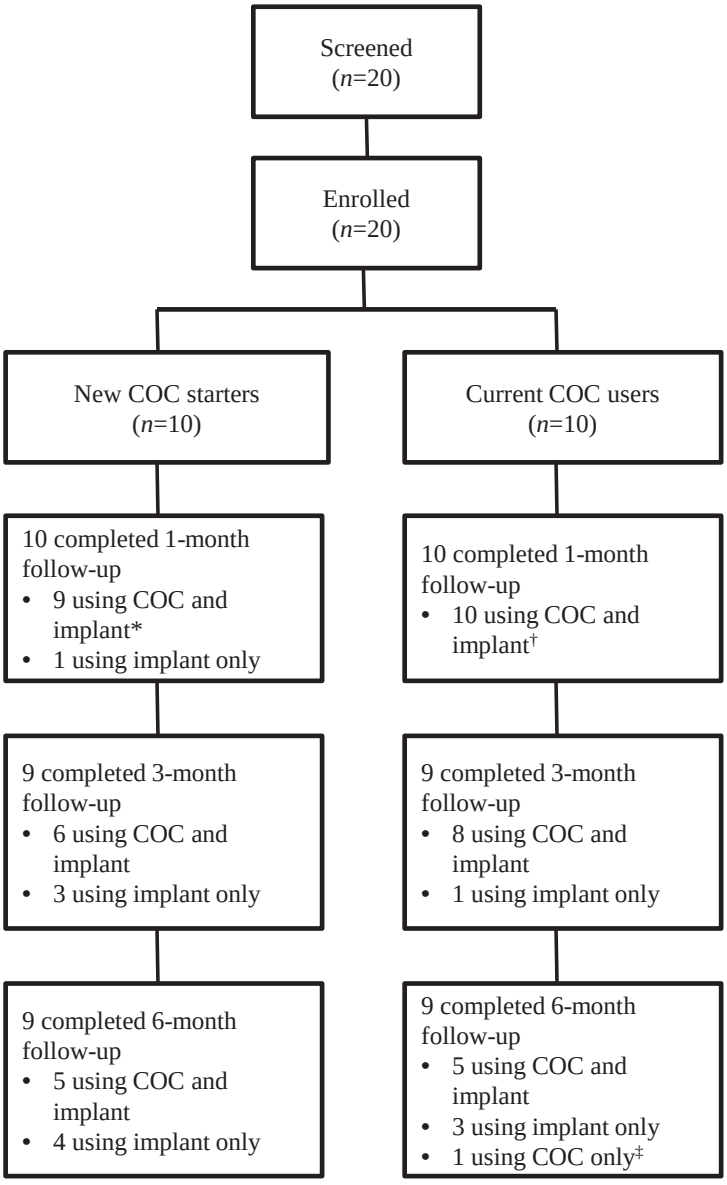
2. Material and methods

We conducted a prospective cohort study of women using COCs who had an etonogestrel implant placed as a "back-up" method to their COCs at the University of California, Davis (UC Davis). The investigators derived the study idea independently of the sponsor prior to applying for funding support. The UC Davis IRB approved the study protocol, and women provided informed consent prior to study participation.

We included women aged 16 years and older planning to initiate or currently using COCs for the primary indication of contraception and were interested in using a contraceptive implant concurrently to further reduce their risk of unintended pregnancy. We classified women *a priori* as "new starters" if the implant was placed four or fewer weeks after COC initiation or who received a COC prescription on the day of implant initiation. We included women as "current pill users" who had been using a COC for more than four weeks prior to implant placement. We excluded women who had contraindications to COC or implant as determined by the Centers for Disease Control Medical Eligibility Criteria for Contraceptive Use [7] and those participating in another clinical trial currently or within the past 30 days.

At the screening visit, we obtained demographic information, past medical and gynecologic history, and current contraceptive use. Participants had the implant placed free of cost once study eligibility was confirmed. Subjects completed daily dairies with bleeding, cramping, pill adherence, and side effects information. Follow-up visits occurred at 1, 3, and 6 months after implant placement. At these visits, we assessed vital signs, weight, side effects, bleeding patterns, and diary completion. Participants could discontinue the implant, COCs, or both at any point in



COC = combined oral contraceptive
* 1 participant lost to follow-up after completing 1-month follow-up
† 1 implant removed at 1-month follow-up, subject subsequently lost to follow-up
‡ Participant had implant removed 4 months after placement and continued COCs only

Fig. 1. Participant flow diagram of contraceptive use at time of follow-up for new starters and current users of combined oral contraceptive pills.

the study. Subjects received up to $150 in remuneration for completion of study visits over 6 months.

We assessed the primary outcomes of implant continuation through six months of study participation and reported side effects of combined COC and implant use. We queried participants specifically on the occurrence of headaches, nausea, vomiting, breast tenderness, mood changes, cramping, acne, and weight changes. Participants also self-reported additional side effects experienced during the study. We classified adverse events as new or worsening side effects. We excluded any side effects related to coincident illness (e.g. food poisoning). Secondary

Table 1
Characteristics of new and current COC users enrolling in study to also use an etonogestrel implant

Characteristic	New COC starters (n = 10)	Current COC users (n = 10)	p-value
Age (years)	25 (20-34)	20.5 (16-34)	0.35
Hispanic ethnicity	3 (30%)	5 (50%)	0.65
Race			
White	6 (60%)	5 (50%)	0.65
Black	1 (10%)	0	
Asian	2 (20%)	3 (30%)	
Other*	1 (10%)	2 (20%)	
Work status			
Employed full-time	3 (30%)	3 (30%)	0.87
Employed part-time	4 (40%)	3 (30%)	
Not employed	3 (30%)	4 (40%)	
Current educational status			
Full-time student	4 (40%)	6 (60%)	0.65
Part-time student	2 (20%)	1 (10%)	
Not current student	4 (40%)	3 (30%)	
Highest level of education attained			
High school or less	0	2 (20%)	0.19
Some college	5 (50%)	6 (60%)	
College degree or higher	5 (50%)	2 (20%)	
Insurance status			
Private	7 (70%)	8 (80%)	0.59
Public	2 (20%)	2 (20%)	
Military	1 (10%)	0	
Current relationship status			
Single	2 (20%)	3 (30%)	0.67
Partnered, living together	2 (20%)	3 (30%)	
Partnered, not living together	6 (60%)	4 (40%)	
Weight			
BMI	24.2 (14.9-32.4)	23.1 (19.5-49.6)	1.0
Obese	3 (30%)	2 (20%)	
Gravidity			
0	6 (60%)	7 (70%)	0.82
1	2 (20%)	1 (10%)	
2 – 3	2 (20%)	2 (20%)	
Parity			
0	6 (60%)	8 (80%)	0.32
1	2 (20%)	2 (20%)	
2	2 (20%)	0	
Duration of COC use (days)	0 (0-19)	684 (30-3972)	<0.01
Pill type			
21/7 monophasic	7 (70%)	5 (50%)	0.64
24/4 monophasic	0	1 (10%)	
21/7 triphasic	1 (10%)	2 (20%)	
Continuous dosing	2 (20%)	2 (20%)	
Progestin type			
Levonorgestrel	5 (50%)	5 (50%)	1.0
Norgestimate	3 (30%)	3 (30%)	
Drospirenone	2 (20%)	2 (20%)	
Secondary reasons for using pills†			
None	1 (10%)	3 (30%)	0.29‡
Bleeding complaints	6 (60%)	2 (20%)	
Acne	3 (30%)	4 (40%)	
Dysmenorrhea	3 (30%)	4 (40%)	
Menstrual flow			
Moderate	5 (50%)	10 (100%)	0.03
Heavy	5 (50%)	0	
Length of menstrual bleeding			
3-5 days	6 (60%)	9 (90%)	0.30
6-7 days	4 (40%)	1 (10%)	
Frequency of menstrual bleeding			
21-35 days	9 (90%)	9 (90%)	0.37
>35 days	0	1 (10%)	
Irregular	1 (10%)	0	

Data presented as n (%) or median (range)
COC = combined oral contraceptive; BMI = body mass index
* Other is comprised of native Hawaiian or Pacific Islander, American Indian, or mixed race
† Participants could choose more than one secondary reason for using pills
‡ Fisher's exact test used for categorical comparison of having a secondary reason for using pills versus none

Table 2
New or worsening side effects reported at follow-up visits by women using COCs and etonogestrel implant

Side effect	1 month*		3 months†		6 months‡	
	New COC starters (n=9)	Current COC users (n=10)	New COC starters (n=6)	Current COC users (n=8)	New COC starters (n=5)	Current COC users (n=5)
Headache	2 (22%)	3 (30%)	1 (17%)	2 (25%)	2 (40%)	0
Nausea	3 (33%)	2 (20%)	2 (33%)	2 (25%)	1 (20%)	0
Vomiting	1 (11%)	0	1 (17%)	1 (13%)	0	0
Breast tenderness	2 (22%)	0	2 (33%)	0	1 (20%)	0
Mood complaints	2 (22%)	4 (40%)	1 (17%)	1 (13%)	1 (20%)	0
Worsening acne	2 (22%)	2 (20%)	1 (17%)	1 (13%)	2 (40%)	0
Worsening dysmenorrhea	1 (11%)	4 (40%)	2 (33%)	1 (13%)	2 (40%)	1 (20%)
Weight gain	2 (22%)	4 (40%)	1 (17%)	4 (50%)	2 (40%)	1 (20%)

Data presented as n (%)
COC = combined oral contraceptive
* 1 new COC starter discontinued pills prior to 1-month
† 1 new COC starter lost to follow-up after 1-month and 2 new starters discontinued COCs; 1 current COC user lost to follow-up after 1-month and 1 current COC user discontinued COCs
‡ 1 new starter discontinued COCs after 3-month follow-up; 2 current COC users discontinued COCs and 1 current COC user discontinued implant after 3-month follow-up

outcomes included COC continuation over six months, plan to continue the implant after six months, and bleeding patterns. We assessed subjective bleeding patterns and analyzed bleeding diaries using World Health Organization (WHO) definitions [8], with regular bleeding as a pattern that did not meet WHO criteria for amenorrhea, prolonged bleeding, frequent bleeding, infrequent bleeding, or irregular bleeding.

For this proof-of-concept study exploring the feasibility of initiating the etonogestrel implant as a "back-up" contraceptive method to COCs, we planned to enroll 20 participants, aiming for 10 new starters and 10 current pill users. We used SPSS 24 (IBM, Armonk, NY, USA) for statistical analysis. We conducted comparisons between groups with Fisher's exact and chi-square tests and considered $p<0.05$ as statistically significant.

3. Results

3.1. Participant characteristics

We consented and enrolled 20 women for study participation between September and December 2016. All participants completed 1-month follow-up and 18 (90%) subjects completed the 3- and 6-month follow-up assessments (Fig. 1). New starters and current pill users had similar characteristics except for menstrual flow and duration of COC use (Table 1). None had previously used an implant. Seven of 10 new starters initiated pill use on the same day as implant placement and two had started the pill within six days of implant initiation. All current pill users had been using pills for greater than 200 days except for one participant (30 days).

3.2. Implant continuation at 6 months

During the 6-month study period, no new starters had the implant removed. Among current pill users, one had implant removal at the 1-month follow-up visit due to mood changes and pain at implant site; she was subsequently lost to follow-up. Another participant had implant removal at four months for mood changes and acne. Overall, two of 19 (10.5%) women for which we had adequate follow-up to assess implant continuation had the implant removed by the 6-month follow-up visit (Fig. 1).

3.3. Side effects reported with COC and implant use

Both new starters and current pill users reported bothersome side effects with using both pills and implant (Table 2). Most side effects occurred infrequently or intermittently (e.g. headaches). About one-third of all participants noted subjective weight gain, and women had an overall median weight increase of 5.3 pounds over six months, with a range of -6.4 to 18.2 pounds. However, only one subject (new starter, removal at six months) discontinued the implant for weight gain. No serious adverse events or pregnancies occurred in either study group.

Women also described improvement in dysmenorrhea and acne during study participation, even among current pill users. A decrease in acne was reported in 3 (15%), 4 (22%), and 1 (11%) participants at 1, 3, and 6-months, respectively. Dysmenorrhea improved throughout the study period with 4 (20%), 5 (28%), and 8 (44%) participants reporting improvement at 1, 3, and 6-months, respectively.

3.4. COC continuation over 6 months

In total, seven women discontinued their COCs during the 6-months of follow-up and relied only on the implant. Among women who completed follow-up through 6 months, new starters used their COCs for a median of 119 days (range 9-179) and current COC users continued pills for a median of 168 days (range 25-180).

3.5. Implant continuation past 6 months

Three new starters elected to discontinue the implant at the 6-month final follow-up visit; one requested removal due to weight gain and acne, one for mood changes, and one for decreased libido. All eight of the current pill users with implants in place at the 6-month visit elected to continue the implant past six months.

3.6. Bleeding patterns

The most common bleeding patterns were infrequent or irregular bleeding (Fig. 2). Few women reported subjective worsening of overall

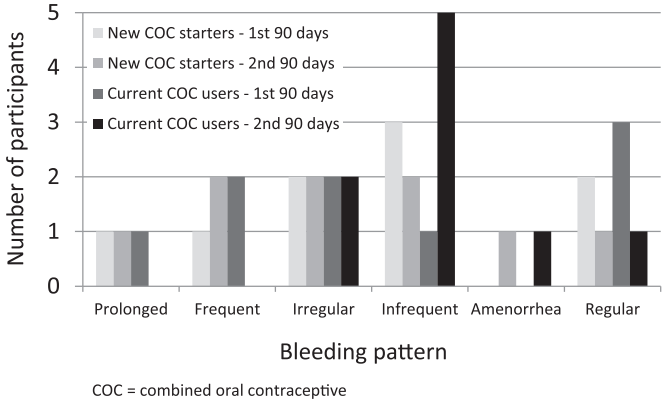


Fig. 2. Bleeding patterns in 90-day intervals of new starters and current users of combined oral contraceptive pills.

Table 3
Subjective assessment of overall bleeding pattern at 3- and 6-month follow-up visits in women using a COC and etonogestrel implant

	New COC starters		Current COC Users	
	3 months	6 months	3 months	6 months
All participants*	n = 9	n = 9	n = 9	n = 9
No change	5 (56%)	3 (33%)	4 (44%)	4 (44%)
Improvement	2 (22%)	4 (44%)	5 (56%)	3 (33%)
Worsening	2 (22%)	2 (22%)	0	2 (22%)
COC and implant users	n = 6†	n = 5†	n = 8†	n = 5‡
No change	4 (66%)	2 (40%)	4 (50%)	4 (80%)
Improvement	0	2 (40%)	4 (50%)	1 (20%)
Worsening	2 (33%)	1 (20%)	0	0

Data presented as n (%)
COC = combined oral contraceptive
* One subject in each group did not provide subjective bleeding data
† The other participants stopped the COC during the interval between visits and were using implant only
‡ The other participants included 3 using implant only and 1 using COC only

bleeding patterns at 3 and 6 months (Table 3), and none of the participants requested implant removal for bleeding complaints.

4. Discussion

In this proof-of-concept study, we were able to successfully enroll COC users to initiate the implant as a "back-up" contraceptive method. Implant continuation rates at six months, our primary outcome, exceeded 80%. Continuation past six months occurred in 74% of COC users including 6/10 new and 8/9 continuing users. Additionally, 7 (39%) women also discontinued pills and relied solely on the implant for contraception. These findings are similar to a previous partially randomized patient preference trial demonstrating that women seeking short-acting methods were willing to try a long-acting reversible contraceptive (LARC) method (i.e. agreed to randomization) [9]. These investigators also demonstrated that women randomized to LARC had higher method continuation at one year after initiation and lower unintended pregnancies compared to women using short-acting methods [9].

Using two methods of hormonal contraception poses concern for an increase in side effects; however, our findings suggest that most women find using both COCs and an implant tolerable. No serious adverse events occurred during the study period, and the frequency of reported side effects did not increase with continued use. Previous studies also demonstrate the overall tolerability of dual use of implant with short courses of a levonorgestrel-containing COCs [5,6]. This study provides safety and side effect data for combined COC and etonogestrel implant use over the longest duration of use published to date (i.e. six months), which is also important for clinicians prescribing COCs to manage bothersome bleeding in women with implants. We could not evaluate any relationships between progestin-type and side effects or bleeding profile in this small study. Continued evaluation of this concept with a larger population may be able to determine whether a specific progestin is better tolerated when used simultaneously with the etonogestrel implant.

Previous studies of women with bothersome bleeding with implant use showed bleeding cessation using a 14-day course of COC [5] or "significant" improvement in bleeding after four weeks of COC use [6]. In our study with much longer concomitant COC and implant use, participant diaries illustrate a range of bleeding patterns from amenorrhea to prolonged bleeding, indicating that initiating the implant can still affect bleeding patterns even in women who had regular bleeding with COCs. These findings suggest that while participants using COCs and implant may experience a subjective improvement in bleeding, they may not have regular bleeding despite concurrent COC use.

Given the small sample size, we cannot make any extensive generalizations about implant uptake among women using COCs outside of a study setting. Some participants may have already been interested in the implant, so were more likely to enroll in the study and continue the method. We attempted to avoid this situation by only screening and enrolling women who indicated they desired COC use as their primary contraceptive method. Regardless, the ability to use both COCs and implant may have been the inciting factor for some women to initiate the implant.

Initiating the implant as a "back-up" method may be an ideal option for women who choose COCs for the non-contraceptive benefits or bleeding profile but desire a more effective contraceptive method. Our findings demonstrate the proof of this new concept and provide the basis for further studies to confirm the long-term acceptability and tolerability of this approach.

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