Official title:

Treatment of unfavorable bleeding patterns in contraceptive implant users: a randomized clinical trial of curcumin

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NCT No:
04205929

Protocol Version Date:
October 15, 2019

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Background:
The etonogestrel (ENG) subdermal contraceptive implant (ENG implant) is a highly effective method of preventing pregnancy, but it has bleeding side effects that make it unappealing for many women. Given that the ENG implant is 20 times more effective at pregnancy prevention than oral contraceptive pills, strategies to increase its acceptability will translate into improved prevention of unplanned pregnancies [1]. Many medications have been studied with progestin-only contraceptives such as the ENG implant to manage irregular bleeding. Concurrent use of oral contraceptives (OCs) with the implant does stop bleeding but bleeding returns when OCs are stopped [2, 3]. The only study to demonstrate a sustained reduction in bleeding lasting for two months was the selective estrogen receptor modulator (SERM) tamoxifen in users of the levonogestrel (LNG) contraceptive implant [4]. We conducted a small clinical trial to evaluate the effects of a 7-day course of tamoxifen in users of Nexplanon© with bothersome breakthrough bleeding, and demonstrated that tamoxifen treatment reduces bleeding/spotting days during the first 30 days after use as compared to placebo [5]. Recently, we successfully completed a study that expanded on our original tamoxifen work and found similar results over a 90-day time period (Merck IIS, paper under development).

We have proven that tamoxifen is a successful strategy to stop breakthrough bleeding in implant users but providers and patients do have concerns about this particular drug since it is used for cancer. Tamoxifen also has a small increased risk of venous thromboembolism (VTE) with continuous use in a menopausal population. Healthly reproductive-age woman with short-term exposure to tamoxifen have not been shown to have a risk of VTE but the concern is still present as well as the stigma that it is a 'cancer' drug. If another agent without these concerns could be found to improve bleeding in implant users then this drug might be more widely adopted.

The exact mechanism of progestin-induced bleeding is unknown but it is likely multi-factorial with the end result of angiogenesis, 'leaky' fragile vasculature, and inflammation. Curcumin, the active ingredient in turmeric, has been demonstrated to be anti-inflammatory, anti-proliferative, and anti-angiogenic which may make it an ideal agent for the management of break-through bleeding. The FDA has determined curcumin is safe and categorizes it as 'generally regarded as safe' (GRAS). Studies have demonstrated that curcumin is extremely well-tolerated. Curcumin has a significant body of evidence as an adjunct treatment in patients with cancer, cardiovascular disease and auto-immune/inflammatory conditions. In terms of women's health, curcumin was better than placebo in a randomized control trial in attenuating the severity of

PMS symptoms but has not been studied for uterine bleeding. Anecdotally, naturopaths and herbalists use it for treatment of heavy menstrual bleeding.

[1] Winner B, Peipert JF, Q Z, C B, Madden TE, Allsworth JE, et al. Effectiveness of Long-Acting Reversible Contraception. New England Journal of Medicine 2012;366:1998–2007.
[2] Guiahi M, McBride M, Sheeder J, Teal S. Short-term treatment of bothersome bleeding for etonogestrel implant users using a 14-day oral contraceptive pill regimen: a randomized controlled trial. Obstet Gynecol 2015; 126: 508-13
[3] Hou MY, McNicholas, C, Creinin MD. Combined oral contraceptive treatment for bleeding complaints with the etonorgestrel contraceptive implant: a randomized controlled trial. Eur J Contracept Reprod Health Care 2016; 21:361-6.
[4] Abdel-Aleem H, Shaaban OM, Amin AF, Abdel-Aleem AM. Tamoxifen treatment of bleeding irregularities associated with Norplant use. Contraception 2005;72:432–7.
[5] Simmons K, Edelman A, Fu Rochelle, Jensen JT. Tamoxifen for the treatment of breakthrough bleeding with the etonogestrel implant: a randomized controlled trial. Contraception 2017: 95:198-204.

Hypothesis:

1) In etonorgestrel (ENG) users with troublesome bleeding, daily treatment with curcumin will result in more days of amenorrhea than placebo in a 30-day reference period.

Objectives:

To identify a successful treatment for troublesome bleeding and spotting in users of the ENG contraceptive subdermal implant.

Primary objective:

1. **Total number of amenorrhea days in a 30-day reference period**

Secondary objectives:

1. **Each 30-day reference period outcomes between treatment and placebo (double blind placebo-controlled RCT):**
   a) Total number of bleeding/spotting days
   b) Total number of consecutive bleeding-free days
   c) Total number of spotting days
   d) Total number of bleeding days
   e) Time (days) to stop bleeding
2. **Overall outcomes:**
   a) Drop out
   b) Patient satisfaction with bleeding pattern
   c) Continuation of implant or anticipation of continuation
   d) Side effects

Study design/Clinical Plan:

We are proposing a randomized, double blind placebo-controlled clinical trial over a 30-day reference period for treatment of women experiencing bothersome bleeding while using the ENG contraceptive implant.

The primary outcome of the study will be the total number of amenorrhea days in a 30-day reference period. The study has a number of secondary outcomes (see above, study objectives) focused around the efficacy of oral curcumin to stop bleeding/spotting and for how long.

The intervention will consist of study drug exposure (curcumin or placebo) daily for 30 days. The first dose will be taken at the start of enrollment if the subject is on the 3rd day of active bleeding or if not bleeding, on day 3 of the next bleeding episode. The study will be conducted at Oregon Health & Science University (OHSU) in Portland, Oregon

Each subject's involvement will be up to approximately 60 days as study drug will not be initiated at the time of enrollment unless they are experiencing bleeding/spotting that day and the two prior days to enrollment. Study drug will be started on the 3rd day of an active bleeding episode. If no active bleeding episodes happen in the first 30 days from enrollment then the participant will be withdrawn from the study. The study will require up to 3 in-person study visits [screening (V1), enrollment (V2), and a close out visit or study exit (V3)], as well as a daily response to a text or email message about bleeding and use of study medication. Additional phone and email contact may occur with the participant to ensure clarity of diary entry or completion or to ensure drug initiation and compliance. The electronic diary only takes a few seconds to complete..

Eligibility:

Inclusion:

- English speaking women 15-45 years of age currently using the ENG implant who have experienced frequent or prolonged bleeding while using the device:
  - To be eligible, women will need to have >7 days of continuous bleeding/spotting in the last 30 days, OR 2 or more episodes of bleeding/spotting in the last 30 days.
- Implant use for at least 30 days prior to screening visit.
- Willing to continue using the implant for at least 30 days from study enrollment.
- Access to a reliable cell phone and must be willing to receive and respond to a daily text or email message to assess bleeding and use of study drug
- Implant must be palpable to prove that an ENG implant is in place at time of screening and enrollment.
- Negative gonorrhea/chlamydia screening performed at screening visit

Exclusion criteria:

- Postpartum within six months
- Post-abortion within six weeks
- Currently pregnant
- Currently breast-feeding (to be eligible, must be 4-6 weeks from cessation of breastfeeding)
- Undiagnosed abnormal uterine bleeding pre-dating placement of contraceptive implant
- Bleeding dyscrasia
- Anticoagulation use
- Active cervicitis
- Allergy to curcumin or turmeric
- History of venous thromboembolism
- Current or past breast or uterine malignancy
- Use of P450 pathway inducing drug
- Implant is due to be switched out in 2 months or less from enrollment
- Currently using oral contraceptives in addition to implant (to be eligible, needs to have a 4-6 week washout period)

- Prior pregnancy occurred while Nexplanon/Implanon was in place

Study procedures

Screening (Visit 1, V1). Estimated 1 hour
Eligibility and study consent will be signed at this visit. Baseline demographic information will be collected by interview, including menstrual history, contraception history including timing of implant placement, sexual and pregnancy history, BMI/weight, ethnicity, age, and baseline use of panty liners (as advised by Mishell et al 2007 to avoid confounding data on bleeding/spotting days). A series of questions will be asked to quantify number of bleeding and spotting days and frequency and duration of bleeding episodes over the preceding three months of implant use (or since placement, if less than three months). Current implant use will be confirmed via palpation.

Physical exam including blood pressure check, pelvic examination, urine pregnancy test, cervical cytology evaluation (if not completed within the ASCCP recommended screening interval), and testing for gonorrhea and chlamydia. A baseline assessment of satisfaction with baseline bleeding pattern will also be performed.

Once negative results from the subject's gonorrhea and chlamydia testing are demonstrated, visit 2 can be scheduled (enrollment).

Enrollment (V2), estimated 30 minutes
This visit could be combined with the screening visit. Randomization for part 1 of the study will occur at this visit. Pregnancy test and blood pressure will be performed. The Subject Study Drug Information Handout will be provided and explained. Study drug will be provided. Subject will only start study drug at this visit if they are experiencing an active bleeding episode and this is the 3rd day of bleeding/spotting. Study coordinator will instruct how to start tracking bleeding via text message. Subjects will receive training on the use of the electronic bleeding diary procedures. This includes instruction on use of the text or email message bleeding diary.

End of study (V3), estimated 30 minutes
The final visit will take place approximately 90 days after enrollment or at the time of study withdrawal/exit. Repeat STI testing only if indicated by a change in partners during the study. Vital signs will be performed and a review of bleeding diary, medications, AEs, and health changes. A short satisfaction questionnaire will be performed. Participation is complete after this visit. Unused study drug will be retuned at these visits.

Visit	**Details**
Visit 1-Screening	• Informed consent • Review medications • Confirm implant use • Physical exam with vitals (blood pressure, pulse, weight, height) • Urine pregnancy test • Review eligibility criteria • Gonorrhea and chlamydia test • Pap (if indicated) • Baseline questionnaire

Visit 2– enrollment	• Review bleeding diary with staff • Review medications • Vitals (blood pressure, pulse, weight, height) • Confirm implant use • Receive placebo or study drug and instructions • Review any health changes
Visit 3- end of study	• Urine pregnancy test if indicated • Repeat Gonorrhea and chlamydia test if change in partner occurs during study. • Review medications • Return any unused medication • Vitals (blood pressure, pulse, weight, height) • Confirm implant use • Review bleeding diary with staff • Review health changes • Exit questionnaire

Description of intervention/study drug

Participants will be instructed to begin use of the study medication daily. A study coordinator (SC) will prospectively follow electronic bleeding diaries at a minimum of three times weekly for each individual study subject to ensure data integrity and correct day of drug initiation. Any unused study drug will be counted and returned at the conclusion of the study.

Failure to complete the texting diary will prompt a phone call or email from the SC. If we are unable to reach a subject by phone, email, letter over a 2-week time period, their participation will be terminated. Any data obtained up to this point will be analyzed in accordance to with intention to treat.

Study procedures and data collection other than side effects and AEs will last 30-days from enrollment.

Compensation

Participants will be compensated up to $250 for their participation in this study. Study visit compensation breakdown is as follows:

- Visit 1- Screening: $50
- Visit 2- Enrollment: $50
- Visit 3- Study end $50
- Diary Completion: $100

Subjects will only be compensated for the visits they complete. For example, if a subject withdraws after visit 2, they will only be compensated for those two visits ($50 + $50).

Diary compensation

Diary completion is defined as responding to 1 daily text message per day. A subject can miss up to 2 days of responses in the up to 60-day study period and still receive diary compensation. If a subject misses 3 or more days of diary entry in a given 30 days, they will not receive this

compensation. Study coordinators will be tracking diary responses, and response rates. If a subject withdraws early from the study, they will only receive compensation for visits that they have completed and not the compensation for diary completion.

Sample size

Our primary outcome is the total number of amenorrhea days in a 30-day reference between curcumin and placebo groups. Our prior tamoxifen study demonstrated a 6-day difference in overall amenorrhea days in the first 30-day reference period.

Based on our recent tamoxifen study, a sample size of 44 women allows us to demonstrate a 6-day difference between groups; 80% power at an alpha 0.05 = 22 women per each group. To account for drop out, we have increased the sample size by approximately 30% for a total sample size of 58.

Study drug

Curcumin an active ingredient in the spice Tumeric is a natural polyphenol. It is purported to have multiple health benefits mostly based in its anti-inflammatory and anti-oxidant properties. Curcumin dosing has been demonstrated to be well tolerated in humans up to 12,000mg/day but dosing as a cancer treatment adjunct or as an autoimmune therapy are in the 400-600mg/day range [1,2]. In general, subjects seem to experience no side effects from curcumin but in a dose escalation study to determine safety and tolerability, 7 of 34 subjects experienced headache, rash, and yellow stool. At higher doses, some nausea and diarrhea have also been reported. Curcumin may have a beneficial effect on cholesterol and triglycerides. Curcumin has poor bioavailability and combining it with piperine, a known bioenhancer derived from black pepper, has been shown to improve curcumin bioavailability by 2000% [3]. However, curcumin without a bioenhancer has also demonstrated therapeutic impact in randomized controlled trials. We plan to use Theracurcumin by Immunovites, 600 mg curcumin, as they report quality testing and have combined curcumin with a bioenhancer for improved bioavailability. This product also contains ginger root powder and bioperine (derived from black pepper). (https://immunovites.com/products/theracurmin-hp-max).

Curcumin is considered a supplement by the US Food and Drug Administration. The FDA has determined curcumin is safe and categorizes it as 'generally regarded as safe' (GRAS). Our IRB chair has recommended that we seek the FDA's opinion regarding the need for an IND for this study as curcumin is a supplement. However, this study is not intended to support a significant change in advertising for curcumin. It is also debatable whether its use is for "treatment" of a disorder or a study of the impact of curcumin on biological function.

[1] Esmaily, H.; Sahebkar, A.; Iranshahi, M.; Ganjali, S.; Mohammadi, A.; Ferns, G.; Ghayour-Mobarhan, M. An investigation of the effects of curcumin on anxiety and depression in obese individuals: A randomized controlled trial. Chin. J. Integr. Med. 2015, 21, 332–338.
[2] Lao CD, Ruffin MT, Normolle D, Heath DD, Murray SI, Bailey JM, et al. Dose escalation of a curcuminoid formulation. BMC Complement Altern Med. 2006;6:10.
[3] Shoba, G.; Joy, D.; Joseph, T.; Majeed, M.; Rajendran, R.; Srinivas, P.S. Influence of piperine on the pharmacokinetics of curcumin in animals and human volunteers. Planta Med. 1998, 64, 353–356.

Risks to Subjects

Human Subjects Involvement and Characteristics

Reproductive-aged (15-45 year old), healthy women currently using a contraceptive implant with no contraindications to the study medication and not at risk for or seeking pregnancy will constitute the target population for this study.

All enrollment and clinical evaluations will be performed at OHSU in Portland, Oregon. Gonorrhea and chlamydia testing and pap testing (if indicated) will be sent to the OHSU core lab for routine processing.

Sources of Materials

The sources of research material for the clinical portion of this proposal will be new specimens obtained purely for this research protocol. The study investigators and/or research assistants/nurses will perform all study procedures.

Potential Risks

One risk to taking part in this study is that the study drug may not be effective in helping to treat bleeding.

The study drug is extremely well tolerated even up to extremely high doses and is considered safe by the FDA. At the highest doses, which we are not utilizing here, a few subjects reported nausea and diarrhea.

Some parts of the study may be inconvenient including the text messaging to collect data. These are regular text or email messages and will count towards text messages or data on a subject's cell phone plan. The subject will be asked detailed questions about her bleeding and gynecologic history. Some of these questions may seem very personal or embarrassing. Women may refuse to answer any of the questions that they do not wish to answer.

Adequacy of Protection Against Risk

Recruitment and Informed Consent

Attempts to enroll a diverse study population will be made through placement of IRB approved flyers in the community, community outreach (radio and print ads) and through the availability of foreign language interpreters and research staff. Women may also learn of the study through their routine visits in clinics or by working at OHSU. We also intend to utilize an EPIC Cohort search to identify and contact potential participants via phone, email, letter, and/or MyChart messages. We intend to use REDCap for batch emailing. We also intend to use Trialspark and Google AdWords as well as Facebook and Instagram for community outreach.

Women will be screened for eligibility and if they meet the basic criteria and agree to participate, they will undergo informed written consent. The protocols and consent will be reviewed and approved by the OHSU IRB prior to initiation of the study.

Protection Against Risk

The drug utilized in this study will be used in accordance with dose and routes that the FDA has determined to be safe. Women will be informed that they will be using a supplement and this is not an FDA approved drug but that we have specifically chosen a dose and length of exposure time to the drug or compound with extremely low potential for significant side effects or serious risks. Women will undergo screening for any known contraindications to the study drugs.

Confidentiality of personal health information will be maintained according to HIPAA requirements for research. All subjects will receive a study number to which all subsequent data will refer. Personal identifiers will not be on questionnaires, data, abstract sheets, or in the main database. All data will be kept in locked files or a password protected computer in the Principal Investigator's (PI) office.

Data and safety monitoring of plans for clinical trials

The PI and study staffs are responsible for recording the data, and they will be verifying its accuracy throughout the process. The PI will be reviewing the data in-depth upon completion of the study. The PI will also be overseeing that the study procedures are being carried out as per the approved protocol via close supervision of study visits and procedures and through frequent communication with the study staff. The PI will also be conducting an initial assessment and periodic assessments of the study and its procedures. If any safety concerns arise, a data safety monitoring board will be convened to review the study. As this study will be performed in conjunction with the Women's Health Research Unit's (WHRU), an independent chart audit to ensure data integrity and completeness will be performed after the first 5 subjects have been enrolled and then at regular 6 months intervals.

The PI will adhere to OHSU's Institutional Review Board (IRB) policies regarding protection of human subjects and the reporting of study deviations and adverse events. In the rare case of an adverse event, she will utilize the WHRU data safety monitoring board (DSMB) to review the event and rule on a course of action. The WHRU DSMB is made up of individuals knowledgeable about women's reproductive health and therapies and will have no conflict of interest with the study or its outcomes.

Data Storage

Data for this project will be stored in OCTRI's installation of REDCap, a highly secure and robust web-based research data collection and management system.

Features of REDCap that protect participants' privacy and data security include:

- Physical Security: OCTRI's REDCap software is housed on servers located in ITG's Advanced Computing Center providing locked physical security
- Electronic Security: The REDCap servers are housed behind both the OHSU firewall and a second ACC firewall. All web-based data transmissions are encrypted with industry-standard SSL methods.
- Controlled User Access: REDCap is employs a robust multi-level security system that enables researchers to easily implement "minimum necessary" data access for their research staff, including specification of data fields that are identifiers. This feature includes "single click" ability to provide completely deidentified (removing all identified data fields and shifting dates) for analysis or other purposes. User activities are logged to enable auditing of all data access. Access is integrated with OHSU's network such that users who are also OHSU employees are authenticated against their OHSU network credentials.
- Data Integrity: REDCap is jointly managed in accordance with OHSU Information Security Directives by ACC staff and members of OCTRI's Biomedical Informatics

Program, ensuring fidelity of database configuration and back-ups. User activities are logged to enable auditing of all data changes.

Data Sharing

We intend to use “Box” to share study documents and spreadsheets.

Potential Benefits of the Proposed Research to the Subjects and Others

There are no direct benefits to study participants.

Importance of Knowledge to be Gained

This study will increase the knowledge regarding breakthrough bleeding and contraceptive implants. It may help to prolong continuation of contraceptive implant use which in turn could help women avoid unplanned pregnancies.