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Tamoxifen for the treatment of breakthrough bleeding with the etonogestrel implant: a randomized controlled trial☆,☆☆

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Abstract

Objective: The etonogestrel (ENG) subdermal implant can cause frequent breakthrough bleeding in some users. The objective of this study was to evaluate whether a short course of tamoxifen reduces bleeding/spotting days compared to placebo in ENG implant users.
Study design: In this double-blind trial, we randomized ENG implant users with frequent or prolonged bleeding or spotting to tamoxifen 10 mg or placebo twice daily for 7 days, to be started after 3 consecutive days of bleeding/spotting. Treatment was repeated as needed up to three times in 180 days. Subjects completed a daily text message bleeding diary. A sample size of 56 provided 80% power to detect a difference of 6 days of bleeding/spotting per 30 days by two-sample *t* test. Ovulation was monitored by urinary metabolites of progesterone.
Results: From March 2014 to February 2015, 56 women enrolled. Fifty-one completed at least 30 days of follow up, and 34 completed 180 days. Compared to women randomized to placebo, women randomized to tamoxifen reported 5 fewer days of bleeding/spotting over 30 days (95% confidence interval [CI] −9.9 to −0.05, p=.05), and 15.2 more continuous bleeding-free days (95% CI 2.8–27.5 days, p=.02) after first use of study drug. Conclusions could not be drawn after 30 days due to higher-than-expected dropout. No ovulation was detected.
Conclusion: First use of tamoxifen by ENG implant users reduces bleeding/spotting days and provides a longer cessation of bleeding/spotting than placebo, without compromising ovulation suppression. Further study is needed to determine whether this effect is maintained with repeat use.
Implications: Women with frequent ENG implant-related breakthrough bleeding may experience a reduction in bleeding/spotting days and an increase in continuous bleeding-free days in the month following first use of tamoxifen. This short course of tamoxifen was well tolerated with bleeding cessation noted within a median of 5 days.

Keywords: Etonogestrel implant; Breakthrough bleeding; Contraception; Tamoxifen

1. Introduction

The etonogestrel (ENG) contraceptive implant is a highly effective method of reversible contraception, but it can cause frequent breakthrough bleeding (BTB) in some users [1,2]. Bleeding pattern changes, particularly increased frequency of bleeding, are the most commonly cited reasons for implant discontinuation [3]. A reliable treatment for BTB should increase acceptability and continuation of this highly effective contraceptive.

No pharmacologic therapy has demonstrated a prolonged reduction in BTB with the ENG implant [4]. Though combined oral contraceptive pills (COCs) are usually effective in terminating an episode of bleeding with the ENG implant, bleeding returns rapidly upon discontinuation,

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potentially requiring long-term cotherapy to maintain an acceptable bleeding profile [5]. Mifepristone may reduce BTB with ENG implants, but it has limited availability and could theoretically impair the contraceptive properties of the implant through antagonism of the progesterone receptor [4]. By contrast, a 10-day course of the selective estrogen receptor modulator tamoxifen provided a sustained reduction in BTB in users of levonorgestrel (LNG) implants [6]. Women who received tamoxifen reported fewer days of bleeding and spotting than women taking placebo during the 2 months after treatment (6.2 vs. 12.3 days in month one, p=.0003; 6.8 vs. 11.9 days in month two, p=.0008). This bleeding reduction after tamoxifen was associated with higher satisfaction and less implant discontinuation than placebo [4,6].

The objective of this study was to determine whether tamoxifen reduces BTB in users of the ENG implant. We hypothesized that tamoxifen would reduce BTB and increase satisfaction without compromising ovulation suppression.

2. Materials and methods

2.1. Study participants

This randomized, double blind, placebo-controlled trial was conducted at Oregon Health & Science University (OHSU) in Portland, OR, USA, from March 2014 to August 2015. The Institutional Review Board at OHSU approved the study protocol. All participants completed written informed consent prior to any study procedures.

We used provider referrals and radio advertisements to recruit 15–45-year-old women using the ENG 68-mg subdermal implant (Implanon/Nexplanon, Merck, Kenilworth, NJ, USA) for at least 30 days. Women were invited to participate after a phone screen if they met criteria for frequent or prolonged bleeding or spotting during the past month. *Frequent* was defined as bleeding/spotting (B/S) more than every 24 days, and *prolonged* was defined as B/S every day in a row for 14 days or longer, consistent with prior study populations [1,7,8]. All reported bleeding was treated as BTB, as the ENG implant suppresses ovulation and normal menstrual cyclicity, such that no scheduled bleeding is expected [1]. Exclusion criteria included postpartum within 6 months, postabortion within 6 weeks, breast-feeding, undiagnosed abnormal uterine bleeding predating placement of the implant, bleeding dyscrasia, anticoagulation use, active cervicitis, history of venous thromboembolism, history of breast or uterine malignancy and other contraindication to tamoxifen. Subjects were not permitted to use COCs for management of BTB during participation.

2.2. Procedures

After telephone screening, subjects completed an enrollment visit for collection of baseline information including menstrual, contraception, sexual and pregnancy histories, race/ethnicity, age and baseline use of panty liners for BTB [9]. To quantify baseline B/S, research assistants used a calendar to help subjects estimate the number of bleeding, spotting and bleeding-free days over the preceding month. Subjects completed a visual analog scale (VAS) (0–100 mm) to assess satisfaction with current bleeding pattern. Trained research nurses performed a physical exam including blood pressure, height/weight, pelvic examination, urine pregnancy test, cervical cytology evaluation (if indicated) [10] and screening for gonorrhea and chlamydia.

Subjects received the first bottle of study drug during the enrollment visit, either 10-mg tamoxifen or identical placebo capsule to be taken twice daily for 7 days. Participants were instructed to start study drug the next time they experienced 3 consecutive days of B/S (initiating drug on the third day) or immediately if they had been B/S for at least 3 days in a row at the time of enrollment. The OHSU research pharmacy assigned the intervention during the enrollment visit in a 1:1 fashion using a computer-generated random allocation rule [11]. The pharmacy maintained the randomization scheme and treatment assignments in a locked cabinet. Study staff and participants had no access to the allocation sequence and were blinded to treatment assignments. The randomization code was broken after completion of all data collection and entry.

Subjects completed bleeding and study drug diaries on paper and over text message starting on the day of enrollment. They responded to an automated daily text message (Mir3, San Diego, CA, USA) using single digits to code their bleeding, with bleeding defined as a day that required the use of protection with a pad, tampon or liner and spotting as a day with minimal blood loss that did not require the use of any protection [9]. A second single-digit response indicated use of study drug (yes/no). If a subject did not respond to the text message for 3 sequential days, she was contacted by phone, email and, finally, certified letter to troubleshoot technical difficulties and ensure continuation of participation. A subject was considered lost to follow-up after 2 weeks of no contact. We included B/S responses for these subjects until they stopped responding.

Subjects returned for follow up visits 14 days after completing study drug, at which time they returned unused drug, received a new bottle if indicated and reported satisfaction and side effects. Participation lasted until a final visit at 180 days or until an early termination visit. Subjects were permitted to use the study drug up to three times over 180 days, each time triggered by 3 days in a row of B/S, with at least 30 days between uses. The selection of three drug courses over 180 days was made based on the 60-day effect duration reported previously [6].

To determine whether tamoxifen affects ovulation suppression, we asked subjects to collect first morning urine samples for 14 days after initiating the first course of study drug, freeze the samples in their home freezer (−20 °C), and bring the samples to the next scheduled study visit. Urine samples were thawed, aliquoted, refrozen at−20 °C and