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Vaginal estrogen supplementation during Depo-Provera initiation: a randomized controlled trial

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Abstract

Background: Irregular bleeding is often cited as the reason for discontinuation of depot-medroxyprogesterone acetate (DMPA) after the first injection. Estrogen supplementation during DMPA initiation may decrease bleeding and improve continuation.
Study Design: This prospective, randomized, controlled trial evaluated estrogen supplementation during DMPA initiation. Women initiating DMPA were randomized to receive an estradiol vaginal ring for 3 months versus DMPA alone. Bleeding diaries and questionnaires at three and 6 months assessed bleeding, continuation and ring acceptability.
Results: Seventy-one participants enrolled; 49 completed the first follow-up period. The median number of bleeding or spotting days was 16 in the estrogen ring group (n=26) versus 28 in the DMPA alone group (n=23) (p=.19). Seventy-seven percent of the intervention group received a second injection compared with 70% in the DMPA alone group (p=.56). For each additional day of bleeding and/or spotting reported, women were 3% less likely to receive a second injection (OR 0.97, 95% CI 0.94–0.99). Acceptability of the vaginal ring was high among those in the intervention group.
Conclusions: Vaginal estrogen supplementation during DMPA initiation is acceptable to women and may decrease total bleeding.

Keywords: Depot medroxyprogesterone acetate; Irregular bleeding; Estradiol vaginal ring; Contraceptive continuation

1. Introduction

Over 2 million American women used depot medroxyprogesterone acetate (DMPA) for contraception in 2002 [1]. DMPA offers the advantage of long-acting, highly effective contraception and requires less frequent administration than other reversible hormonal methods such as the pill, ring, or patch. Approximately 30% of users discontinue after the first injection [2–6]. One study of a very young, largely Hispanic, urban population demonstrated 60% discontinuation after the first injection [7]. Irregular bleeding is one of the most common reasons cited for discontinuation [3–6,8].

Irregular bleeding is most prevalent in the first 90 days of DMPA use and the mean number of bleeding or spotting days steadily decreases during the first year of use [9,10]. The mechanism of irregular bleeding in DMPA users remains poorly understood. A growing body of basic science research suggests that long-term use of progestin-only contraception leads to changes in local milieu of regulatory molecules including vascular endothelial growth factor, angiopoeitins 1 and 2, and tissue factor, decreased uterine perfusion, blood vessel fragility and aberrant angiogenesis [11–15]. It is unclear how estrogen supplementation might affect this pathophysiologic process.

In DMPA and Norplant users who presented with complaints of prolonged bleeding in two randomized trials (n=278 DMPA and n=131 Norplant), ethinyl estradiol was more effective than placebo in decreasing the time to cessation of bleeding as well as mean number of bleeding days [16,17]. Use of transdermal estradiol in post-abortion patients initiating DMPA did not increase continuation at 1 year but protocol adherence was suboptimal [18].

We sought to identify an acceptable intervention that would decrease bleeding during the first 3 months of DMPA use and improve continuation. A vaginal ring that releases 100 mcg of estradiol per day and is designed for 90 days of consecutive

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use is currently approved for use in postmenopausal women. Here we present the results of a randomized controlled trial of estrogen supplementation through a vaginal ring versus no supplementation during the first 3 months of DMPA use. We hypothesize that the estradiol vaginal ring will be acceptable to participants and will decrease bleeding during the first 3 months of DMPA use and increase continuation at 3 months.

2. Methods and materials

This study is a prospective, randomized, controlled, non-blinded trial that recruited participants at a Title X Family Planning Clinic in New York City. Women who presented to clinic seeking DMPA for contraception were eligible to participate if they were at least 18 years old, spoke English or Spanish and had not used DMPA or a levonorgestrel intrauterine system in the preceding 120 days. Women reporting oligomenorrhea (defined as fewer than 4 periods in the last 6 months), amenorrhea, or contraindications to either DMPA or estrogen were excluded. Each participant provided written informed consent prior to randomization. The randomization sequence, with a 1:1 allocation ratio, was generated by a staff member not involved with the study and enclosed in sequentially numbered opaque envelopes. After obtaining consent, a research assistant opened the envelope to reveal group assignment. This study was approved by the Columbia University Institutional Review Board and registered with clinicaltrials.gov.

On the day of enrollment, all participants completed a baseline questionnaire to collect sociodemographic information and contraceptive, reproductive and menstrual history. Each participant received DMPA 150 mg intramuscular injection per clinic protocol. Those randomized to the intervention group also underwent placement of an estradiol vaginal ring intended to be retained for 3 months. Because we were unable to obtain placebo vaginal rings, blinding of participants and investigators was not possible. The vaginal ring is a flexible, off-white ring with an outer diameter of 56 mm, cross-sectional diameter of 7.6 mm, and core diameter of 2 mm. The central core of the ring contains 24.8 mg of estradiol acetate which releases at a rate equivalent to 0.1 mg of estradiol per day for 3 months. The in vivo delivery rate of estradiol is approximately 0.01 mg of estradiol per day over 3 months [19].

Participants were followed up for a total of 6 months. Each participant kept a daily diary to record bleeding, spotting, or absence of bleeding. Study personnel called participants weekly to keep a shadow diary. After approximately 3 months of use, participants returned for a follow-up visit. At this visit, we provided remuneration for time spent on weekly phone calls, diary completion and travel to visits; collected bleeding diaries; removed the vaginal ring; and administered a questionnaire to assess acceptability, perceptions of bleeding and continuation of DMPA. Shadow diaries were compared with participant diaries with minimal discrepancy noted. Participants were provided with a second injection of DMPA or their choice of contraception at this visit. Willing participants continued to keep bleeding diaries for another 3 months regardless of their method choice. At the 6-month follow-up visit, we again provided remuneration, collected bleeding diaries, administered a final questionnaire and provided the participant with her choice of contraception.

The primary objective of this study was to determine whether participants in the intervention group reported fewer days of bleeding and/or spotting. Secondary outcomes included acceptability of the ring and rates of continuation at three and 6 months. Bleeding and spotting were defined in accordance with World Health Organization definitions that were outlined and updated in recently published consensus guidelines [20,21]. Bleeding and spotting were measured through daily diaries and reported as mean number of days, median number of days, range of days, mean number of bleeding/spotting episodes and mean number of days per episode. Acceptability was measured through a series of questions assessing participant willingness to use the ring again or recommend it to a friend, comfort, ease of removal, ease of replacement and overall satisfaction. We also recorded the number of participants who removed the ring prior to completion of the first follow-up visit. Continuation was measured as the proportion of participants receiving a second and third injection.

Based on a large WHO trial (n=748), we assumed that the control group would experience a mean of 24 days of bleeding and/or spotting (S.D. 19) during the first 90 days of DMPA use [22]. To detect a 14-day reduction in mean number of bleeding and/or spotting days in the intervention group with a 5% probability of type I error and 20% probability of type II error, 30 participants were required in each group. Accounting for 20% anticipated loss to follow-up, we set our sample size at 72 participants.

This analysis includes all participants who completed the first follow-up period and those who received a second injection of DMPA and completed follow-up through 6 months. An intention-to-treat analysis is reported here with participants analyzed in their originally assigned group regardless of duration of vaginal ring use; we also carried out a pre-protocol analysis. Baseline characteristics, bleeding and continuation in the intervention and control groups were compared using chi-square tests, t tests, or Mann-Whitney U tests. We describe acceptability of the ring among intervention group participants who completed the first follow-up period. Logistic regression was used to identify variables associated with continuation in the baseline population. Statistical analyses were performed using SAS 9.2.

3. Results

Of 249 women screened, 100 (40%) were ineligible for enrollment (Fig. 1). The most common reasons for ineligibility