Contraception xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Contraception

journal homepage: www.elsevier.com/locate/con

Original research article

# Continuous dosing of a novel contraceptive vaginal ring releasing Nestorone® and estradiol: pharmacokinetics from a dose-finding study☆,☆☆

J.T. Jensen [a,*], A.B. Edelman [a], B.A. Chen [b], D.F. Archer [c], K.T. Barnhart [d], M.A. Thomas [e], A.E. Burke [f], C.L. Westhoff [g], L.S. Wan [h], R. Sitruk-Ware [i], N. Kumar [i], B. Variano [i], D.L. Blithe [j]

[a] Department of Obstetrics & Gynecology, Oregon Health & Science University, Portland, OR
[b] Department of Obstetrics, Gynecology & Reproductive Sciences, Magee-Womens Research Institute, University of Pittsburgh School of Medicine, Pittsburgh, PA
[c] Department of Obstetrics and Gynecology, Eastern Virginia Medical School, Norfolk, VA
[d] Pennsylvania Clinical Research Center, Department of Obstetrics & Gynecology, University of Pennsylvania School of Medicine, Philadelphia, PA
[e] Reproductive Medicine Research, Department of Obstetrics & Gynecology, University of Cincinnati College of Medicine, Cincinnati, OH
[f] Department of Gynecology and Obstetrics, The Johns Hopkins University School of Medicine, Baltimore, MD
[g] Department of Obstetrics & Gynecology, Columbia University College of Physicians and Surgeons, New York, NY
[h] Department of Obstetrics & Gynecology, New York University School of Medicine, New York, NY
[i] Center for Biomedical Research, Population Council, New York, NY
[j] Contraceptive Development Program, Eunice Kennedy Shriver National Institute of Child Health and Human Development, Bethesda, MD

ARTICLE INFO

*Article history:*
Received 11 October 2017
Received in revised form 8 January 2018
Accepted 23 January 2018
Available online xxxx

*Keywords:*
Contraceptive vaginal ring
Nestorone
Estradiol
Pharmacokinetics
Contraception
Continuous cycling

ABSTRACT

*Background:* As part of a program to develop a novel estradiol-releasing contraceptive vaginal ring (CVR), we evaluated the pharmacokinetic (PK) profile of CVRs releasing segesterone acetate (Nestorone® (NES)) combined with one of three different estradiol ($E_2$) doses.

*Study design:* A prospective, double-blind, randomized, multi-centered study to evaluate a 90-day CVR releasing NES [200 mcg/day] plus $E_2$, either 10 mcg/day, 20 mcg/day, or 40 mcg/day in healthy reproductive-age women with regular cycles. Participants provided blood samples twice weekly for NES and $E_2$ levels during the first 60 days (ring 1) and the last 30 days (ring 2) of use. A subset underwent formal PK assessments at ring initiation, ring exchange (limited PK), and study completion.

*Results:* The main study enrolled 197 women; 22 participated in the PK substudy. Baseline characteristics between the main and PK participants were comparable, with an average BMI of 25.8 kg/m$^2$ (SD 4.3). In the PK substudy, all three rings showed similar NES PK: mean area under the curve ($AUC_{(0–72)}$) 34,181 pg*day/mL; concentration maximum ($C_{max}$) 918 pg/mL; time to maximum concentration ($T_{max}$) 3.5 h. For $E_2$, the $C_{max}$ occurred at 2 h, and was significantly higher with the 20 mcg/day ring (mean 390 pg/mL); 10 mcg/day, 189 pg/mL, p=.003; 40 mcg/day, 189 pg/mL, p<.001), and declined rapidly to≤50 pg/mL for all doses by 24 h. For all subjects, the median $E_2$ levels remained under 35 pg/mL during treatment.

*Conclusion:* PK parameters of NES were not affected when paired with different doses of $E_2$, but $E_2$ levels from all three doses were lower than anticipated and no dose response was observed.

☆ Authors Disclosures: Dr. Jensen has received payments for consulting and research support from Bayer Healthcare, Merck, Agile Therapeutics, Abbvie, HRA Pharma, Teva, and the Population Council, consulting only from MicroChips and Evofem, and research support only from Estetra SPRL and Medicines360. These companies and organizations may have a commercial or financial interest in the results of this research and technology. These potential conflicts of interest have been reviewed and managed by OHSU. Dr. Edelman: consultant for World Health Organization, CDC, Gynuity Health Projects, Genzyme, and Agile Therapeutics. Nexplanon trainer for Merck. Author for UptoDate (Royalties received). Research funding from Merck and National Institutes of Health (NIH). Dr. Sitruk-Ware is an employee of the Population Council, a not for profit organization, IND holder for Nestorone formulations, and developer of the vaginal ring described in this paper. Dr. Blithe is an employee of the NIH and involved in a CRADA with HRA Pharma. Dr. Chen has received research support through Agile Therapeutics, Bayer Healthcare, Medicines360, and Merck, all managed through the Magee-Womens Research Institute, and is on a Merck advisory board. Dr. Burke receives research support from Bayer and the OC OTC Working Group, through Johns Hopkins.Dr. Thomas has received research support through Agile Therapeutics, Bayer Healthcare, and Medicines 360, all managed through the University of Cincinnati College of Medicine.

☆☆ Financial Support: Support for this research was from NICHD Contraception Clinical Trial: Network HHSN275200403378I (OHSU); HHSN 275201300019I (EVMS); HHSN 275201300020I (UPenn); HHSN27521100043U (UPitt); HHSN275201300002I (NYU); HHSN275201300004I (JHU); HHSN275201300010I (Columbia). The authors also acknowledge grant support from the National Institutes of Health for the OHSU Oregon Clinical & Translational Research Institute (NIH NCRR 1 UL1 RR024120), the Bioanalytical Shared Resource/Pharmacokinetics Core at OHSU, the Biomarkers Core Laboratory of Columbia University's Irving Institute for Clinical and Translational Research (NIH UL1 TR000040), and the work conducted at the Population Council. The content of this publication is the sole responsibility of the authors and does not necessarily represent the official views of the NIH.

* Corresponding author. Tel.: +1 503 346 5425; fax: +1 503 494 3111.
*E-mail address:* jensenje@ohsu.edu (J.T. Jensen).

https://doi.org/10.1016/j.contraception.2018.01.012
0010-7824/

*Implications:* While these novel estradiol-releasing combination contraceptive vaginal rings provided sustained release of contraceptive levels of Nestorone over 90 days, the $E_2$ levels achieved were not consistent with bone protection, and a dose–response was not observed.



## 1. Introduction

Unintended pregnancies adversely impact a woman's life, health, and wellbeing, and contribute to our world's exponential population growth which is detrimental to the environment. Successful development of contraceptive methods that are highly effective, safe, easy to adhere to, and acceptable to women is essential to counteracting this public health crisis. Reversible methods with longer-acting duration, in contrast to the need for daily, weekly or monthly dosing, have grown in popularity, and their widespread use has been shown to directly decrease unplanned pregnancy and abortion rates within a population [1].

Long-acting reversible contraceptive (LARC) methods require a skilled health care provider for placement and removal. A woman-controlled long-term reversible method would present a novel delivery system. A vaginal ring delivery system releasing segesterone acetate (Nestorone® (NES)), a 19-norprogesterone derivative that binds selectively to progesterone receptors and not androgen receptors [2–4], combined with ethinyl estradiol (EE) designed for use over thirteen cycles (one year) has been tested for safety, efficacy, and bleeding profile [5–7]. This ring provided high efficacy and acceptability similar to existing shorter-acting combined hormonal methods but with the opportunity for longer-term dosing with a single product.

Although NES is not orally active, it is very potent transvaginally and is highly effective at suppressing ovulation [8,9]. EE induces hepatic protein synthesis and clotting factors when given orally, transdermally and transvaginally; therefore, ring administration provides no safety advantage to existing products [10,11]. In contrast, 17β-estradiol ($E_2$) does not appear to increase the risk of thrombosis when delivered transdermally at physiologic doses, at least when studied in postmenopausal women [12]. Utilizing $E_2$ rather than EE as the estrogen component in a CVR could improve the safety of combined hormonal contraception in regard to thrombosis risk. Continuous use of the ring may help improve adherence (missed or late next ring use) and thus increase effectiveness.

We present the pharmacokinetic (PK) parameters from a Phase IIa dose-finding study of a 90-day vaginal ring dosed continuously releasing 200 mcg/day NES and either 10, 20, 40 mcg/day of $E_2$. These doses were specifically chosen based on previous studies supporting the ongoing CVR development program at the Population Council. Several doses of NES have been evaluated [13] with a dose of 150 mcg/d selected for development of the NES/ethinyl estradiol (EE) CVR [A New Drug Application for this CVR is currently under review by the US Food and Drug Administration (press release, Population Council: http://www.popcouncil.org/news/population-councils-one-year-contraceptive-ring-advances-to-fda-review)]. Given that the estrogen component of a combined hormonal contraceptive contributes to ovarian suppression [14,15], we assumed that higher levels of NES would be required for full ovarian suppression with an E2 CVR, due to the lower potency of E2 compared with EE. This led us to select the 200 mcg/d release for this NES/E2 vaginal ring. When selecting the dose of E2, previous studies demonstrated a less favorable bleeding profile when lower doses of NES, up to 100 mcg/d were used in combination with higher levels of E2 (>45 mcg/day) in a CVR [unpublished data, Population Council]. Our goal was to achieve ovulation suppression with NES while preventing hypoestrogenism with $E_2$.

## 2. Materials and methods

We conducted a prospective multi-centered, double-blind, randomized, Phase IIa dose-finding study sponsored and developed jointly by the Population Council (NY, NY) and the Contraceptive Discovery and Development Branch, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD; Bethesda, MD). Eight NICHD Contraceptive Clinical Trials Network (CCTN) (Eastern Virginia Medical School, University of Pennsylvania, University of Pittsburgh, Johns Hopkins University, Oregon Health & Science University (OHSU), University of Cincinnati, New York University, and Columbia University) participated in the study from April 2012 to December 2013. Participants at the OHSU site only were offered the option of participation in a detailed PK substudy. The respective sites' Institutional Review Boards approved the study protocol and all participants underwent written informed consent. The trial was registered with clinicaltrials.gov (NCT0158600).

Sites recruited healthy, reproductive-aged (18–39 years old) women not at risk for pregnancy (e.g. same-sex partner, heterosexually abstinent, use of a non-hormonal method of contraception or male partner with vasectomy if heterosexually active) and willing to abstain from non-water-based vaginal lubricants during the study. Main inclusion criteria included regular menstrual cycles, intact uterus and ovaries, BMI<35 kg/m$^2$, no recent use of hormonal contraception, no contraindications to combined hormonal contraception, no use of drugs known to interfere with the metabolism of sex steroids, and smoking<15 cigarettes/day if age<35 or no smoking if age 35 or greater. Once enrolled, women underwent a control cycle (Cycle 1), a treatment period equivalent to six 30-day cycles (Cycles 2–7) and then one post-treatment cycle (Cycle 8). Health Decisions (Research Triangle, NC) provided central randomization for all sites using a computer-generated randomization schedule with random permuted blocks. The OHSU Research Pharmacy provided a separate computer-generated randomization schedule for the PK substudy.

Subjects were randomized 1:1:1 to receive one of three CVRs developed to release NES 200 mcg/day and either 10 mcg/day, 20 mcg/day, or 40 mcg/day of $E_2$. The Population Council formulated the silicone elastomer contraceptive vaginal rings (CVR) utilized in this study using a proprietary technology. The overall mean (56.4 mm) and cross-sectional (8.2 mm) diameter of the rings and color (white) did not differ with dose. Each study ring was used for a duration of 3 months (90 days); and subjects used 2 consecutive rings of the same dose over the course of the study (no hormone-free interval). Subjects self-inserted and removed rings during an in-person visit at the study site: Ring 1 between days one and five during Cycle 2, removed at day 90 and replaced by Ring 2, in turn removed on day 180. Subjects received instructions to not remove the ring during the study, including during sexual activity. Subjects recorded compliance with ring use and bleeding events using a paper daily diary; the study coordinator reviewed this at each visit. End of study participation was determined by a subject experiencing a second episode of spontaneous bleeding after ring removal.

All participants underwent twice weekly blood draws during the control cycle, the first 60 days of Ring 1, the week prior to the ring exchange, and the last 30 days of Ring 2 use. PK substudy subjects additionally completed full PK assessments at initiation of Ring 1 [accumulation PK; 0 (ring placement), 2, 4, 6, 8, 10, 12, 24, 48 and 72 h] and removal of Ring 2 [elimination PK; 0 (ring removal), 2, 4, 6, 8, 10, 12, 24, 48 and 72 h], and a limited PK evaluation during the exchange of Ring 1 to Ring 2 [0 (ring exchange), 2 and 24 h]. Site staff allowed blood samples to clot, used a refrigerated centrifuge to separate serum, and stored serum aliquots at -80C prior to shipment to the central labs for analysis.

### 2.1. Assay characteristics

The Biomarkers Core Laboratory of Columbia University's Irving Institute for Clinical and Translational Research (New York, NY, USA) performed the $E_2$ analysis following liquid–liquid extraction with

Please cite this article as: Jensen JT, et al, Continuous dosing of a novel contraceptive vaginal ring releasing Nestorone® and estradiol: pharmacokinetics from a dose-findin..., Contraception (2018), https://doi.org/10.1016/j.contraception.2018.01.012