Return to Fertility After Use of the 1-Year Segesterone Acetate/Ethinyl Estradiol Contraceptive Vaginal System

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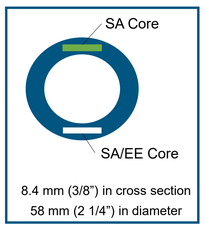
Introduction

- A contraceptive vaginal system (CVS) developed by the Population Council was approved by the FDA as Annovera in August 2018 (**Figure 1**)
  - One-year, ring-shaped CVS designed to release an average daily dose of 0.15 mg segesterone acetate (SA) and 0.013 mg ethinyl estradiol (EE)
- The SA/EE CVS is an effective hormonal contraceptive that can potentially address a common access issue in many regions with its unique advantages:[1,2]
  - A single CVS can be used in a 21/7-day in/out cyclic schedule for up to one year (13 cycles of 28 days) and the cyclic regimen allows for regular bleeding patterns[3]
  - The CVS is a woman-controlled method as it can be inserted and removed by the user without the aid of a trained health care provider
  - Refrigeration is not required for CVS storage before dispensing or during cyclic non-use periods

Figure 1. Depiction of the SA/EE contraceptive vaginal system



Objective

To assess the return to menses and/or fertility in a subset of women who used the 0.15 mg SA/ 0.013 mg EE CVS for up to 13 cycles

Methods

- The 0.15 mg SA/0.013 mg EE CVS was evaluated in two multicenter, single-arm, open-label, pivotal, phase 3 studies, with one US-only study (NCT00455156) including 15 sites and one international study (NCT00263341) including 5 sites in the US, 3 in Europe, 3 in Latin America, and 1 in Australia[1,2]
- Participants were women who were 18–40 years old, healthy, sexually active with a prior history of regular menstrual cycles
- Women were instructed to use the same SA/EE CVS following a 21-days-in, 7-days-out schedule for up to 13 cycles (one year) with appropriate washing between cycles
  - Any removal of the CVS during the 21-day, day-in period was not to exceed 2 hours, and participants were to record dates when the CVS was in or out and durations of CVS removal if >2 hours
- After completion of the SA/EE CVS efficacy study, women who wished to use non-hormonal contraceptives or desired pregnancy could enter a 6-month post-treatment follow up for return-to-fertility assessment
  - A urine pregnancy test was to be taken within 2–3 weeks following the last study visit and then monthly if experiencing pregnancy symptoms and/or not having a bleeding episode
- Follow-up data on pregnancy, menses, and contraceptive use was monitored every 2 months for up to 6 months
  - Women with a positive pregnancy test were asked to return to the clinic for pregnancy confirmation and prenatal care referral
- Return to fertility was defined as pregnancy within 6 months post CVS use or spontaneous menses that occurred at least 18 days after last CVS use
  - Bleeding occurring <18 days after CVS use was considered withdrawal bleeding rather than menses
- Proportion of subjects who reported menses and/or pregnancy in the return-to-fertility population was calculated

Results

Disposition of the Return-to-Fertility Population

- Of the 370 women who entered the 6-month return-to-fertility follow up from the two phase 3 studies, 317 (85.7%) were able to be contacted (**Figure 2**)
  - 27 women were excluded from the return-to-fertility follow-up study because they used hormonal contraceptives, leaving 290 women for analysis

Assessment of Return to Fertility

- All 290 women included in the return-to-fertility analysis reported a pregnancy or a return to regular menses during the 6-month follow up, indicating a 100% incidence of return to fertility (**Table 1**)[1]
- Of the 38 subjects who desired pregnancy, 24 (63.2%) became pregnant within 6 months after last CVS use[1]
  - Women who reported pregnancy had a mean age of 27.3 years (range, 19–38 years), similar to those of the phase 3 study population (26.7 years)[1,2]
  - Duration of their CVS use ranged from 132 to 381 days, with an average of 293 days

Figure 2. Participant disposition for return-to-fertility assessment in the two phase 3 studies

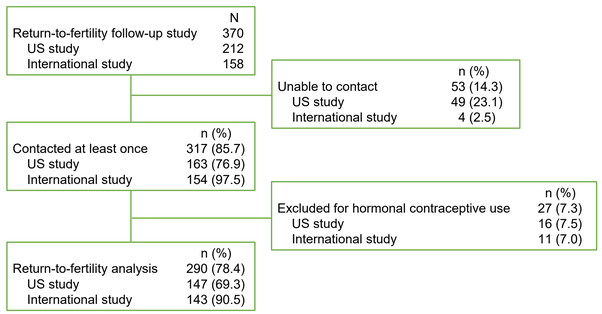


Table 1. Proportion of subjects who reported pregnancy or post-treatment menses

n (%)	US study (n=147)	International study (n=143)	Total (n=290)
Pregnancy	12 (8.2)	12 (8.4)	24 (8.3)
Spontaneous menses	135 (91.8)	131 (91.6)	266 (91.7)
Total return to fertility	147 (100.0)	143 (100.0)	290 (100.0)

Time to Pregnancy During the 6-Month Follow up

- Of the 12 pregnancies in the US study, 6 were reported at 2 months, 3 at 4 months, 2 at 6 months and 1 at >6 months (woman reported her pregnancy at an additional unscheduled follow-up call)
- In the international study, 6 of the total 12 pregnancies were reported at 2 months, 5 at 4 months, and 1 at 6 months
- For the 24 women who became pregnant, the estimated mean time from CVS removal to pregnancy was 81 days (range, 18–187 days), with half of the pregnancies occurring within 60 days after last CVS use (**Table 2**)

Table 2. Estimated time to pregnancy after CVS use

Time, days	US study n (%)	International study n (%)	Total n (%)
All	12	12	24
1–30	1 (8.3)	1 (8.3)	2 (8.3)
31–60	6 (50.0)	4 (33.3)	10 (41.7)
61–90	1 (8.3)	3 (25.0)	4 (16.7)
91–120	1 (8.3)	2 (16.7)	3 (12.5)
121–150	2 (16.7)	1 (8.3)	3 (12.5)
151+	1 (8.3)	1 (8.3)	2 (8.3)

Conclusions

- All women who desired pregnancy or used non-hormonal contraceptives after CVS use reported a return of fertility, defined as a return to normal menses and/or pregnancy within 6 months after last CVS use
  - This suggests that the use of 0.15 mg SA/0.013 mg EE CVS does not delay or adversely affect return to fertility
- Annovera (SA/EE CVS) provides an effective, safe, procedure-free, women-controlled, easily accessible contraceptive method that may be suitable to address contraceptive needs worldwide

References

1. Archer DF, et al. *Lancet Glob Health*. 2019;7:e1054-e1064. **2.** Gemzell-Danielsson K, et al. *Contraception*. 2019;99:323-328. **3.** Vieira CS, et al. *Contraception*. 2019; https://doi.org/10.1016/j.contraception.2019.07.145

Disclosures

- GDC consults to multiple pharmaceutical companies including but not limited to Population Council and TherapeuticsMD and has stock options from TherapeuticsMD. KTB consults to AbbVie and Bayer Healthcare. AEB has received research support from Bayer Healthcare, Ibis Reproductive Health, and NICHD (managed through Johns Hopkins University). RBM is an employee of Population Council, a not-for-profit research organization. SG, BB, and SM are employees of TherapeuticsMD with stock/stock options. BB is also a Board member of TherapeuticsMD.
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