Bleeding Patterns with a 1-Year, Segesterone Acetate/Ethinyl Estradiol Contraceptive Vaginal System

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Introduction

- Acceptability of any contraceptive method depends on the efficacy, safety, and side-effect profile[1,2]
- Favorable bleeding profiles are an important factor influencing contraceptive choice and adherence to a particular method[1,2]
- Irregular bleeding with combined hormonal contraceptives can diminish satisfaction and potentially lead to irregular use or discontinuation[3,4]
  - Inconsistent use can amplify bleeding problems
- A novel 1-year, ring-shaped contraceptive vaginal system (CVS) with the progestin, segesterone acetate (SA) and ethinyl estradiol (EE) (Annovera™; licensed to TherapeuticsMD, Boca Raton, FL) was approved by the FDA (August 2018)
  - Reusable for 13 cycles (one year) on a 21-day in/7-day out regimen
  - Does not require refrigeration before first use or during cyclical periods of nonuse

Objective

To characterize scheduled and unscheduled bleeding with the SA/EE CVS and identify factors associated with unscheduled bleeding/spotting (B/S)

Methods

- We pooled data for this analysis from two identically designed multicenter, single arm, open-label pivotal phase 3 trials assessing the SA/EE CVS at 27 sites located in the US (20), Latin America (3), Europe (3) and Australia (1)
- Healthy, sexually active women aged 18-40 years used a single CVS releasing SA 0.15 mg and EE 0.013 mg per day following a 21-day in/7-day out schedule of use for up to 13 cycles
- Participants recorded daily vaginal bleeding and spotting for each 28-day cycle in paper diaries (**Table 1**)

Table 1. Bleeding criteria used by subjects and investigators in SA/EE CVS phase 3 trials

Bleeding criteria used by subjects	Description
None	No bleeding or spotting
Spotting	Small amount of bloody discharge not requiring sanitary protection
Normal bleeding*	Sanitary protection used
Heavy bleeding*	Bleeding more than usual during a woman's regular menses
Bleeding categories for analysis	**Description**
Scheduled B/S (ie, withdrawal bleeding)	Any B/S during the CVS-out period (days 22 to 28 of each cycle), which could have continued uninterrupted into days 1 to 4 of the next cycle
Unscheduled B/S	Any B/S while using the CVS (days 1 to 21 of the cycle)†
Amenorrhea	No scheduled or unscheduled B/S at any time during 13 cycles

*Normal and heavy bleeding were analyzed together as one group; †With the exception of B/S reported during days 1 to 7 of the first cycle of CVS insertion or withdrawal bleeding that continued into days 1 to 4 in subsequent cycles.

- We used multiple logistic regression to examine associations between the number of unscheduled B/S episodes and participant age, body mass index (BMI), ethnicity, race, education, and smoking during the first 4 cycles only

Results

- 2278 participants enrolled; 2070 women had daily bleeding diary data for cycle control analysis
- Only 1.7% of subjects discontinued early due to unacceptable bleeding
- Mean age and BMI of participants were 26.7 ± 5.1 years and 24 ± 3.6 kg/m^2, respectively; most were aged 20 to 29 years (**Table 2**)

Table 2. Demographic and baseline characteristics of subjects

Characteristic	Participants (N=2070) n (%)
Age, y	
18-19	122 (6)
20-24	771 (37)
25-29	680 (33)
30-35	361 (17)
≥ 36	136 (7)
BMI, kg/m^2	
< 25	1373 (66)
≥ 25	697 (34)
Ethnicity	
Hispanic or Latina	593 (29)
Not Hispanic or Latina	1477 (71)
Race	
White	1500 (73)
Black/African-American	281 (14)
Other/Unknown	289 (14)
Education (highest level)	
College degree or higher	889 (43)
Some college	674 (33)
High school diploma/equivalent	378 (18)
Less than high school	129 (6)
Current Smoking	302 (15)

BMI: body mass index.

Scheduled Bleeding

- 97.9% of women had scheduled B/S during the 7-day out period in ≥1 cycle during the 13 cycles of CVS use (**Figure 1**)
- Overall mean ± SD number of scheduled B/S days was 4.9 ± 1.1 and bleeding-only days was 3.3 ± 1.0
- Absence of scheduled B/S was 5% to 8% of women/cycle

Unscheduled Bleeding

- 29.3% of women experienced ≥1 episode of unscheduled bleeding
  - 5.4% to 10.0% reported unscheduled bleeding in any cycle (**Figure 2**)
- 56.3% of women experienced ≥1 episode of unscheduled B/S
  - 13.2% to 21.7% reported unscheduled B/S in any cycle (**Figure 2**)
- For women with unscheduled B/S, overall mean ± SD of unscheduled B/S days were 3.9 ± 2.8 and bleeding-only days of 3.3 ± 2.0
- 44 (0.9%) participants reported complete amenorrhea during any cycle (ie, no B/S at any time); 2.6% to 4.9% reported amenorrhea per each cycle

Figure 1. Participants with any scheduled B/S

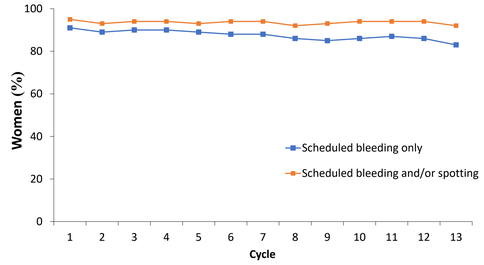
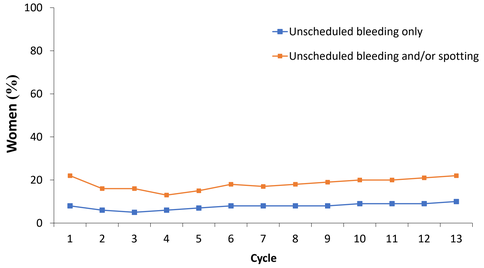


Figure 2. Participants with any unscheduled B/S



Demographic Factors Associated with Bleeding

- Ethnicity and race were significantly associated with unscheduled B/S (**Table 3**)
  - Compared with white women, black/African-American women were more likely to report unscheduled/spotting (OR 1.49; 95% CI, 1.14-1.94)
- Age and BMI did not influence bleeding patterns

Table 3. Associations between participants' characteristics and unscheduled B/S episodes in the four first cycles of SA/EE CVS use

	No episodes n (%)	Unscheduled B/S n (%)	P-value*
n	902	1168	
Age, y			0.12
18-19	60 (6.6)	62 (5.3)	
20-24	336 (37.2)	435 (37.2)	
25-29	291 (32.3)	389 (33.3)	
30-35	168 (18.6)	193 (16.5)	
≥36	47 (5.2)	89 (7.6)	
BMI, kg/m²			0.49
<25	608 (67.4)	765 (65.5)	
≥25	294 (32.6)	403 (34.5)	
Ethnicity			**0.003**
Hispanic	278 (30.8)	315 (27.0)	
Not Hispanic	624 (69.2)	853 (73.0)	
Race			**0.01**
Black	101 (11.2)	180 (15.4)	
White	672 (74.5)	828 (70.9)	
Other/Unknown	129 (14.3)	160 (13.7)	
Education			0.09
≥College degree	363 (40.2)	526 (45.0)	
Some college	294 (32.6)	380 (32.5)	
High school diploma	178 (19.7)	200 (17.1)	
<High school	67 (7.4)	62 (5.3)	
Current Smoking			0.59
Yes	125 (13.9)	177 (15.2)	
No	777 (86.1)	991 (84.8)	

BMI: body mass index; CVS: contraceptive vaginal system.*P-value by Pearson Chi-Square. Bleeding and/or spotting episode = bleeding/spotting days bound on either end by 2 days of no bleeding or spotting.

Summary and Conclusions

- Participants using the SA/EE CVS for up to 13 cycles experienced cycle control consistent with most other combined hormonal contraceptives with a planned hormonal withdrawal bleeding every 28 days
- Unscheduled bleeding remained stable over the course of the study
- Discontinuation rate due to unacceptable bleeding (1.7%) was very low
- Further research into associations between demographics and bleeding is warranted
- The bleeding profiles experienced by women using the SA/EE CVS may provide appropriate guidance for clinicians who counsel women about their expectations with contraceptive options, as well as provide reassuring information for prospective users

Disclosures

- ALN consults for or is on the advisory board of Agile Therapeutics, AMAG, Bayer Healthcare, ContraMed/Sebela, Cooper Surgical, Merck, and Pharmanest; received research support from Estetra, EvoFem, FHI (MonaLisa), and Mathra; and has served on the speaker's bureau of Agile Therapeutics, Avion, Bayer Healthcare, Cooper Surgical, and Merck. CSV served/serves on advisory boards and/or as ad hoc lecturer for Bayer Healthcare and Merck. ISF has acted as a Consultant for, chaired Advisory Boards for, given lectures for and received honoraria from Bayer Healthcare, Daiichi Sankyo, Merck (MSD), and Vifor Pharma. AEB received research support from Bayer Healthcare, Ibis Reproductive Health, and NICHD (managed through Johns Hopkins University). MLG has nothing to disclose. VB has nothing to disclose.
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