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Bleeding profile associated with 1-year use of the segesterone acetate/ethinyl estradiol contraceptive vaginal system: pooled analysis from Phase 3 trials☆,☆☆,☆☆☆

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ABSTRACT

Objectives: To describe bleeding patterns among users of the segesterone acetate (SA) and ethinyl estradiol (EE) contraceptive vaginal system (CVS), and identify factors associated with unscheduled bleeding/spotting (B/S).
Study design: We pooled results from two multicenter, single-arm, open-label, pivotal, phase 3 studies of the SA/EE CVS conducted in 17 US and 7 international sites. Participants (age 18–40 years; BMI ≤29 kg/m^2) followed a 21/7-day in/out schedule of CVS use for up to 13 cycles and recorded vaginal bleeding daily in paper diaries. Scheduled and unscheduled B/S were summarized by cycle. We used multiple logistic regression to identify factors associated with unscheduled bleeding/spotting, based on the first 4 cycles only.
Results: Analysis included data from 2070 participants (16,408 cycles). Ninety-eight percent documented scheduled B/S [mean (SD): 4.9 (1.1) days/cycle)]. Absence of scheduled B/S was 5–8% of women/cycle. Unscheduled B/S ranged from 13.2% to 21.7% of women per cycle. Few women (1.8%) discontinued prematurely due to unacceptable bleeding. Black women were more likely to report unscheduled B/S than White women [Adjusted odds ratio (AOR) = 1.49, 95% confidence interval (CI) = 1.14–1.94]. Women with fewer years of schooling [<high school (AOR=0.62, 95% CI=0.43–0.90); high school graduate (AOR: 0.76, 95% CI=0.60–0.97)] were less likely to report any episode of unscheduled B/S compared to college graduates.
Conclusions: Participants using the SA/EE CVS up to 13 cycles reported good cycle control. Discontinuation due to

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☆☆ **Declaration of interest:**

- AB has received research funding from Bayer, Ibis Reproductive Health, and NICHD, managed through Johns Hopkins University.
- CSV has served on the Medical Advisory Boards for Merck and Bayer, and has given ad hoc invited lectures for Merck and Bayer.
- CLW reports grants from Agile Therapeutics, during the conduct of the study; personal fees from Merck, personal fees from Bayer, personal fees from Cooper Surgical, personal fees from Allergan, grants from Estetra SPRL, grants from Leon Farma, grants from Medicines360, outside the submitted work.
- DLB is a principal investigator on a Cooperative Research and Development Agreement between NICHD and HRA Pharma.
- ISF has acted as a Consultant for, chaired Advisory Boards for, given lectures for and received honoraria and expenses from Bayer Healthcare, Merck/MSD, Vifor Pharma and Daiichi Sankyo.
- JJ has received payments for consulting and research support from Abbvie; Bayer Healthcare; Daré; Merck; Sebela, and the Population Council, consulting only from Cooper Surgical, 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.
- LB has served on the Medical Advisory Boards for Merck and Bayer, and has given ad hoc invited lectures for Merck and Bayer.
- MP, RSW, and RM are employees of the Population Council, a not for profit organization, IND holder for segesterone acetate formulations, and developer of the vaginal system described in this paper.

☆☆☆ The other co-authors have no conflicts of interest to disclose.

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unacceptable bleeding was very low. Further research into demographic/other differences with reported unscheduled bleeding is warranted.
Implications: Since good cycle control is a key factor influencing contraceptive selection, adherence and continuation of combined hormonal contraceptives, the favorable bleeding profiles experienced by women during the SA/EE CVS clinical trials provide reassuring information for prospective users.

1. Introduction

Vaginal ring technology can add to the method mix for both contraceptive use and prevention of sexually transmitted infections. The highly vascular vaginal mucosa makes the vagina an excellent route for delivering sustained levels of medications [1,2]. Vaginal rings provide a discreet, easy to use, non-daily and woman-controlled delivery system for contraception [1,3,4].

The Population Council developed a one-year ring-shaped contraceptive vaginal system (CVS) with a formulation that delivers a novel progestin, segesterone acetate (SA), also known as Nestorone® (NES), along with ethinyl estradiol (EE). The novelties of this CVS include being reusable for 13 cycles on a 21/7-day regimen and not requiring refrigeration during cyclical periods of nonuse or prior to first use. The U.S. FDA approved this CVS (Annovera®, Therapeutics MD; Boca Raton, FL, USA) in 2018. The Pearl Index for the primary efficacy group was 2.98 (95% CI 2.13–4.06) per 100 woman-years and was well within the range indicative of efficacy for a contraceptive under a woman's control [5].

Acceptability of any contraceptive method involves efficacy and the side-effect profile [6]. For vaginal ring products, ease of use, expulsions, and effects on sex and intercourse are additional important characteristics [1,3,4,7]. Patient-centered contraceptive counseling should assist women in identifying important method attributes, which may lead to improved satisfaction and continuation with the contraceptive chosen [8].

Menstrual bleeding changes are common when using combined hormonal contraceptives (CHC); such changes can diminish satisfaction and/or willingness to continue using the method [9,10]. Women report that having predictable scheduled bleeding is an important attribute for choosing a CHC [4]. Although scheduled bleeding is the most common bleeding pattern experienced by CHC users, unscheduled bleeding or amenorrhea may also occur [11,12].

Appropriate guidance regarding expected bleeding patterns is a key component of contraceptive counseling [13]. To provide detailed information about bleeding patterns associated with the SA/EE CVS and to identify factors associated with unscheduled bleeding/spotting (B/S), we conducted a pooled analysis of the Phase 3 trials of the SA/EE CVS.

2. Methods

2.1. Study design and setting

This pooled analysis includes data from two identically designed pivotal phase 3 studies of the SA/EE CVS. These trials were multicenter, single arm, open-label studies, conducted from 2006 to 2009 at 27 sites located in the US (20), Latin America (3), Europe (3) and Australia (1). Both studies were registered on ClinicalTrials.gov (NCT00263341, NCT00455156). The efficacy and overall safety aspects of the trial are published separately [5,14].

2.2. Participants

Participants were healthy, sexually active women 18–40 years old with a prior history of regular menstrual cycles (every 28±7 days when not using hormonal contraception; if postpartum or postabortal, history of regular menstrual cycles of 21–35 days in length and resumption of at least one cycle with a cycle length consistent with her past cycles). Exclusion criteria included medical contraindications to CHC use; body mass index (BMI) >29.0 kg/m^2; cystocele, rectocele or any uterine anatomical abnormality; severe constipation; undiagnosed abnormal genital bleeding; known hypersensitivity to any components of the CVS including silicone rubber; monthly injectable contraceptive use within 2 months or depot medroxyprogesterone acetate use within 6 months of study initiation; known or suspected alcoholism or drug abuse; and history of permanent contraception. Women were not enrolled if they chronically used concomitant medications known to induce cytochrome P450 liver enzymes.

The institutional review board (IRB) of the Population Council, one contracted by the National Institute of Child Health and Human Development (NICHD)'s Contraceptive Clinical Trial Network (CCTN) Coordinating Center (Advarra, Columbia, MD 21046), and each participating site's local IRB or Ethical Committee approved the protocol. All potential participants provided written informed consent prior to screening and any study procedures.

2.3. Intervention

Participants used a single CVS releasing 0.15 mg of SA and 0.013 mg of EE daily designed for cyclic use for up to one year (13 cycles). Each cycle included 21 days in which the CVS was in the vagina (CVS-in days) followed by 7 days when the CVS was not in the vagina (CVS-out days). This pattern of use included insertion and removal on the same day of the week and continued for up to 13 cycles.

2.4. Outcomes and assessments

The bleeding profile for up to 13 cycles associated with SA/EE CVS use was the primary outcome for this analysis. Factors associated with unscheduled bleeding and/or spotting in the first 4 cycles of CVS use were secondary outcomes.

Participants' baseline sociodemographic characteristics were collected during screening.

Investigators instructed participants to record and describe any bleeding they experienced each day in a paper diary. Bleeding descriptions based on the World Health Organization (WHO) terminology were: none (no bleeding or spotting), spotting (small amount of bloody vaginal discharge for which the woman did not need to use sanitary protection), normal bleeding (sanitary protection used), or heavy bleeding (bleeding more than usually observed during regular menses) [15,16]. Because the distinction between normal and heavy bleeding may have varied between subjects, the two categories were combined as “bleeding” for this analysis.

We analyzed bleeding profile by the number of bleeding and/or spotting (B/S) days that participants experienced in each cycle of CVS use (defined as 28 days). We defined B/S episodes as any B/S days bounded on either end by 2 days of no bleeding or spotting [15,16].

Scheduled B/S (i.e., withdrawal bleeding) was defined as any B/S that occurred during the CVS-out period (Days 22 to 28 of each cycle). Scheduled B/S may have continued uninterrupted into Days 1–4 of the subsequent cycle. Unscheduled B/S was defined as any B/S that occurred while using the CVS (i.e., Days 1 to 21 of the cycle), except 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 calculated the proportion of participants with scheduled and unscheduled B/S per cycle, as well as the proportion of participants with amenorrhea during CVS use defined as no scheduled or unscheduled B/S at any time during 13 cycles.

We examined associations between the number of unscheduled B/S episodes and participant baseline characteristics (age, ethnicity, race, marital status, education, smoking status, BMI, and parity) in the first 4 cycles of CVS use. Since many participants did not complete all 13 cycles, we included only the first 4 cycles of CVS use for this subanalysis to reduce bias or confounding that could stem from women contributing a varying number of cycles. Another reason for focusing on the first 4 cycles for this subanalysis is that changes in early bleeding patterns can influence contraceptive discontinuation [17].

2.5. Sample size

FDA requirements for Phase 3 safety and efficacy trials of contraceptives containing a new chemical entity determined the sample size, which was consistent with harmonization guidelines from the European Medicines Agency (EMA), i.e., such Phase 3 trials must accrue exposure based on 20,000 treatment cycles of use and include at least 400 women who complete 1 year of treatment [18].

2.6. Statistical analysis

We used descriptive statistics to summarize participant baseline sociodemographic characteristics, and the scheduled and unscheduled B/S by cycle during 1 year of CVS use. For analyses of scheduled B/S, we included only those cycles wherein participants recorded at least 3 days of responses during Week 4 (Days 22–28). Similarly, for analyses of unscheduled B/S, we included only cycles that had at least 15 of 21 days of responses reported in subject diaries during Weeks 1 to 3 (Days 1–21). Cycles in which a pregnancy had occurred were excluded from these analyses. Diary days with missing entries were considered as no B/S, otherwise missing data were not imputed. We performed a sensitivity analysis including only women who reported perfect CVS use.

We used Pearson's χ^2 test to evaluate associations between the number of unscheduled B/S episodes and baseline demographic characteristics. We categorized the number of unscheduled episodes as: no episodes, 1–3 episodes, or ≥4 episodes during the first 4 cycles of CVS use.

To evaluate baseline factors associated with unscheduled B/S episodes during the first 4 cycles, we used a multiple logistic regression model. The initial model included all variables with $p<.25$ (age, ethnicity, race, years of schooling) in the χ^2 analyses. Using backward selection, we sequentially removed variables with the largest p-values, until all remaining variables were significant with $p<.05$. Adjusted odds ratios (AORs) and 95% confidence intervals (CIs) were used to quantify the magnitude and direction of associations.

The level of significance was 5%. We performed all analyses using SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

3. Results

Of 2278 participants enrolled in these trials (20,140 cycles), bleeding diaries from 2070 women contained data for cycle control evaluation for a total of 16,408 cycles (82.2%) in the analysis. Of these 2070 women, 2055 provided diary data on scheduled B/S (i.e., "CVS-out" period), 2068 provided diary data on unscheduled B/S (i.e., "CVS-in" period), and 2052 provided data for both scheduled and unscheduled B/S (i.e., "CVS-in" and "CVS-out" periods).

Table 1 displays the demographic and baseline characteristics of the 2070 participants included in this analysis. The mean ± standard deviation (SD) age and BMI of the participants were 26.7±5.1 years-old and 24±3.6 kg/m^2, respectively. We did not observe differences between participants who had missing diary data (n=1237) and those who did not in terms of age, race or years of schooling (data not shown).

Table 1
Demographic and baseline characteristics of the participants included in the bleeding profile analysis associated with the segesterone acetate/ethinyl estradiol contraceptive vaginal system use

Characteristic	Participants (N=2070) N (%)
Age (years)	
18–19	122 (5.9)
20–24	771 (37.2)
25–29	680 (32.8)
30–35	361 (17.4)
≥36	136 (6.6)
Ethnicity	
Hispanic or Latina	593 (28.6)
Not Hispanic or Latina	1477 (71.3)
Race	
Black/African-American	281 (13.6)
White	1500 (72.5)
Other/Unknown	289 (14.0)
Marital status	
Married	500 (24.1)
Other[1]	1570 (75.8)
Schooling	
College degree or higher	889 (42.9)
Some college	674 (32.6)
High school diploma/equivalent	378 (18.3)
Less than high school	129 (6.2)
Current Smoking	302 (14.6)
BMI (kg/m^2)	
<25	1373 (66.3)
≥25	697 (33.7)
Parity (number)	
0	1358 (65.6)
1–2	598 (28.9)
≥3	114 (5.5)

Participants from pivotal cycle control set (n=2070 women).
1: Divorced, single, separated, widowed, unknown.
BMI, body mass index.

Overall, 97.9% of women experienced scheduled B/S in at least one cycle during the 13 cycles of CVS use. Among women reporting scheduled bleeding, the overall mean ± SD number of scheduled B/S days was 4.9±1.1 days (median: 4.9 days) and the overall mean ± SD number of scheduled bleeding-only days was 3.3±1.0 (median: 3.1 days). The median number of scheduled B/S days and bleeding-only days did not decrease over 13 cycles of SA/EE CVS use among women reporting scheduled bleeding (Fig. 1A). Absence of scheduled B/S ranged from 5.0% to 8% of participants per cycle (Table 2).

Overall, 56.3% of women experienced at least one episode of unscheduled B/S during study participation, with 13.2% to 21.7% of women reporting unscheduled B/S in any cycle (Table 2). Among women reporting unscheduled bleeding, the overall mean ± SD unscheduled B/S days was 3.9±2.8 (median: 3.3 days) and the overall mean ± SD unscheduled bleeding-only days was 3.3±2.0 (median: 3.0 days). The median number of unscheduled B/S days and bleeding-only days remained stable over 13 cycles of SA/EE CVS use among women reporting unscheduled bleeding (Fig. 1B). We conducted a separate analysis of women who documented perfect CVS use, and found that the proportion that experienced unscheduled B/S did not differ more than 2% at any cycle from the results presented in Table 2 (data not shown).

Forty-four (0.9%) participants reported amenorrhea (absent unscheduled and scheduled B/S) during the entire study; the per-cycle reported rate of amenorrhea ranged from 2.6% to 4.9%.

Only 1.8% (37/2070) participants discontinued early due to unacceptable bleeding. Of these, 22 discontinued due to metrorrhagia, 11 due to menorrhagia, and 4 due to another bleeding-related adverse event. The discontinuations among these 37 women occurred between cycles 1 and 13 with a median at cycle 8.

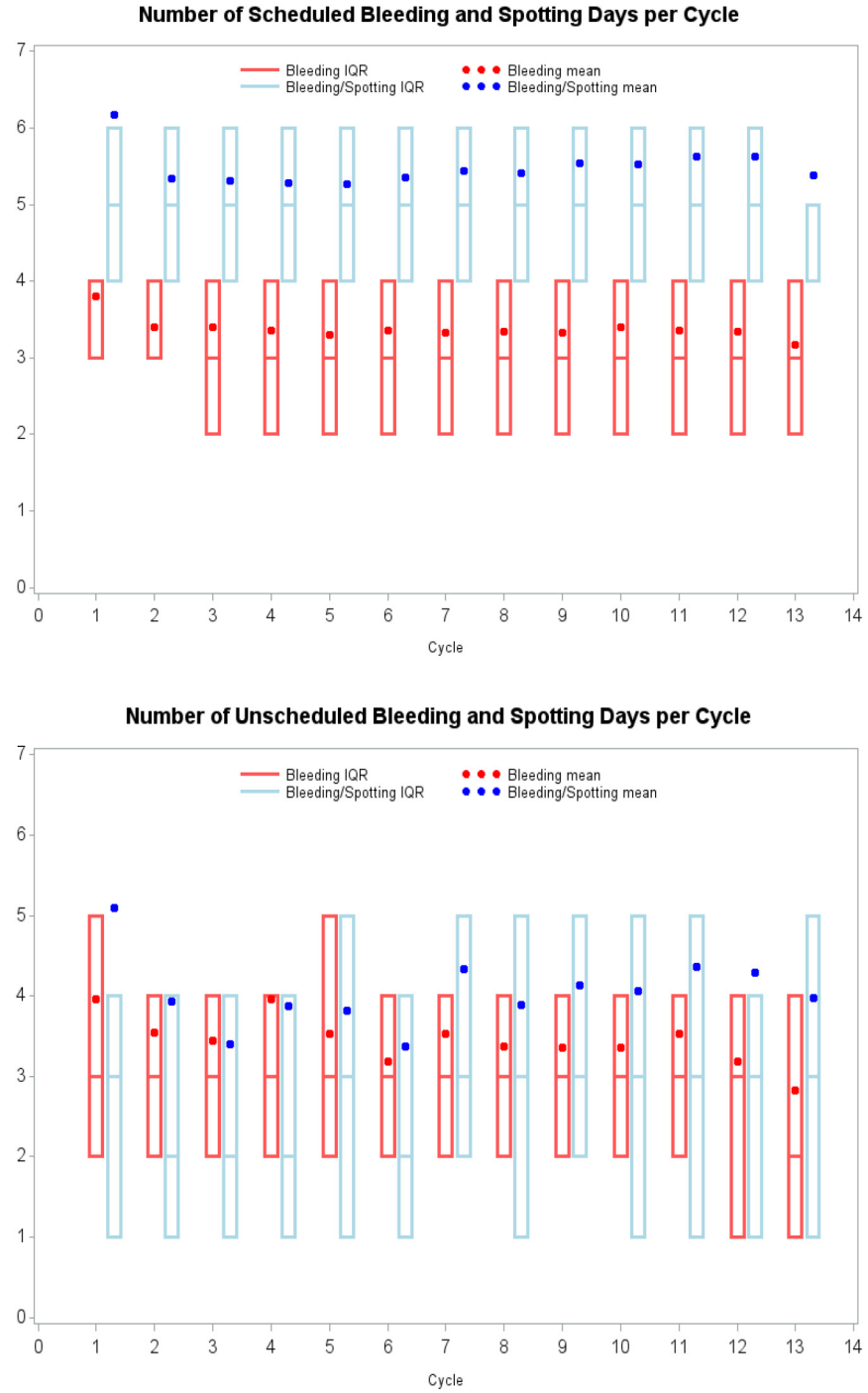

Fig. 1. Number of bleeding/spotting (B/S) days per cycle over 13 cycles of segesterone acetate/ethinyl estradiol contraceptive vaginal system use among women reporting B/S in each cycle.

In the χ^2 analysis, unscheduled B/S was associated with ethnicity (p=.003) and race (p=.01) (Table 3). In addition to ethnicity and race, years of schooling and age were evaluated as predictors in the multiple logistic regression model for having *P*-values <.25.

Table 4 shows that Black women were more likely than White women to report any episode of unscheduled B/S in the first 4 cycles of CVS (AOR=1.49, 95% CI=1.14–1.94). Women with lower educational attainment [< high school (AOR=0.62, 95% CI=0.43–0.90); high school graduated (AOR=0.76, 95% CI=0.60–0.97)] were less likely to report any episode of unscheduled B/S in the first 4 cycles of CVS use (Table 4) compared with women with college degree.

4. Discussion

Results from this pooled analysis document good cycle control with the SA/EE CVS during up to 13 cycles of use. Less than 2% of participants discontinued use of the CVS because of unacceptable bleeding patterns.

Good cycle control is a key factor influencing contraceptive selection, adherence and continuation of CHCs [9]. CHC users select monthly bleeding as one of the most relevant attributes for choosing a contraceptive method [4,19]. Reassurance of the absence of pregnancy, health concerns when women miss a period, plus prevalent beliefs about monthly bleeding as a natural event in a woman's life are common reasons associated with women's preferences for predictable monthly bleeding [10,20].

Table 2
Scheduled and unscheduled bleeding and/or spotting during 13 cycles of segesterone acetate/ethinyl estradiol contraceptive vaginal system use

	Scheduled bleeding[1]			Unscheduled bleeding[2]		
		Bleeding-only	Bleeding/Spotting		Bleeding-only	Bleeding/Spotting
Cycle	**N[3]**	**Any, n (%)**	**Any, n (%)**	**N[3]**	**Any, n (%)**	**Any, n (%)**
1	2020	1840 (91.1)	1908 (94.5)	2029	176 (8.7)	438 (21.6)
2	1744	1558 (89.3)	1625 (93.2)	1754	104 (5.9)	276 (15.7)
3	1509	1355 (89.8)	1423 (94.3)	1520	82 (5.4)	248 (16.3)
4	1456	1313 (90.2)	1372 (94.2)	1460	81 (5.5)	192 (13.2)
5	1406	1248 (88.8)	1312 (93.3)	1417	95 (6.7)	217 (15.3)
6	1259	1104 (87.7)	1177 (93.5)	1267	106 (8.4)	230 (18.2)
7	1214	1064 (87.6)	1138 (93.7)	1214	91 (7.5)	206 (17.0)
8	1174	1013 (86.3)	1085 (92.4)	1178	97 (8.2)	216 (18.3)
9	1022	873 (85.4)	947 (92.7)	1027	83 (8.1)	193 (18.8)
10	932	805 (86.4)	872 (93.6)	939	87 (9.3)	183 (19.5)
11	850	737 (86.7)	798 (93.9)	856	74 (8.6)	172 (20.1)
12	780	673 (86.3)	736 (94.4)	783	69 (8.8)	161 (20.6)
13	649	537 (82.7)	597 (92.0)	713	71 (10)	155 (21.7)
Overall	**2055**	**1991 (96.9)**	**2011 (97.9)**	**2068**	**606 (29.3)**	**1165 (56.3)**

For any cycle, days 22–28 must have at least 3 non-missing B/S responses for it to be included in this analysis. Thus, each N may differ from the unscheduled bleeding analyses.
[1] Scheduled bleeding and/or spotting (i.e., withdrawal bleeding) was defined as any bleeding and/or spotting (B/S) that occurred during the CVS-out period (Days 22 to 28 of each cycle). Scheduled B/S may have continued uninterrupted into Days 1 to 4 of the subsequent cycle.
[2] Unscheduled bleeding and/or spotting was defined as any bleeding and/or spotting (B/S) that occurred while using the CVS (i.e., Days 1 to 21 of the cycle), except 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.
[3] N: total number of participants from pivotal cycle control set analyzed in each cycle. N overall is larger than cycle 1, because some subjects evaluable for later cycles were not evaluable in cycle 1.

Women using the SA/EE CVS exhibited a low incidence of absent scheduled B/S (from 5.0% to 8% per cycle), similar to what has been reported for Nuvaring® [etonogestrel(ENG)/EE vaginal ring] [12,21,22] and monophasic combined oral contraceptives (COCs) used on a daily 21/7 regimen [11,12,23,24]. The number of scheduled B/S days reported by the SA/EE CVS users was comparable to other CHCs [11,21,23,25,26].

Table 3
Associations between unscheduled bleeding and/or spotting episodes in the four first cycles of segesterone acetate/ethinyl estradiol contraceptive vaginal use and study participants' characteristics.

		Unscheduled bleeding/spotting		Total	*p**
	No episodes, n (%)	1–3 episodes, n (%)	≥ 4 episodes, n (%)		
Number of participants	902 (43.6)	833 (40.2)	335 (16.2)	2070	
Age (years)					.12
18–19	60 (6.6)	42 (5.0)	20 (6.0)	122 (5.9)	
20–24	336 (37.2)	317 (38.1)	118 (35.2)	771 (37.2)	
25–29	291 (32.3)	286 (34.3)	103 (30.7)	680 (32.8)	
30–35	168 (18.6)	130 (15.6)	63 (18.8)	361 (17.4)	
≥ 36	47 (5.2)	58 (7.0)	31 (9.2)	136 (6.6)	
Ethnicity					**.003**
Hispanic	278 (30.8)	244 (29.3)	71 (21.2)	593 (28.6)	
Not Hispanic	624 (69.2)	589 (70.7)	264 (78.8)	1477 (71.3)	
Race					**.01**
Black	101 (11.2)	116 (13.9)	64 (19.1)	281 (13.6)	
White	672 (74.5)	601 (72.1)	227 (67.8)	1500 (72.5)	
Other/Unknown	129 (14.3)	116 (13.9)	44 (13.1)	289 (14.0)	
Marital status					.73
Married	224 (24.8)	200 (24.0)	76 (22.7)	500 (24.1)	
Other[1]/Unknown	678 (75.2)	633 (76.0)	259 (77.3)	1570 (75.8)	
Schooling					.09
≥ College degree	363 (40.2)	366 (43.9)	160 (47.8)	889 (42.9)	
Some college	294 (32.6)	276 (33.1)	104 (31.0)	674 (32.6)	
High school diploma	178 (19.7)	142 (17.0)	58 (17.3)	378 (18.3)	
< high school	67 (7.4)	49 (5.9)	13 (3.9)	129 (6.2)	
Current Smoking					.59
Yes	125 (13.9)	123 (14.8)	54 (16.1)	302 (14.6)	
No	777 (86.1)	710 (85.3)	281 (83.9)	1768 (85.4)	
BMI (kg/m^2)					.49
< 25	608 (67.4)	540 (64.8)	225 (67.2)	1373 (66.3)	
≥ 25	294 (32.6)	293 (35.2)	110 (32.8)	697 (33.7)	
Parity (number)					.53
0	599 (66.4)	531 (63.7)	228 (68.1)	1358 (65.6)	
1–2	251 (27.8)	256 (30.7)	91 (27.2)	598 (28.9)	
≥ 3	52 (5.8)	46 (5.5)	16 (4.8)	114 (5.5)	

Bleeding and/or spotting episode: Bleeding/spotting days bounded on either end by 2 days of no bleeding or spotting.
1: Divorced, single, separated, widowed.
BMI: Body Mass Index; CVS: Contraceptive Vaginal System.
* P value by Pearson χ^2 Square.

Table 4
Factors associated with having any episode of unscheduled bleeding and/or spotting in the first four cycles of segesterone acetate/ethinyl estradiol contraceptive vaginal system use.

	Total (2070)	≥4 episodes (335)	Adjusted OR*	95% CI	p Value
	N	***n* (%)**			
Race					**.01**
Black	281	180 (28.3)	1.49	1.14–1.94	
Other/unknown	289	160 (55.4)	1.03	0.80–1.33	
White	1500	828 (55.2)	ref	-	
Schooling					**.03**
<High school	129	62 (48.1)	0.62	0.43–0.90	
High school diploma	378	200 (52.9)	0.76	0.60–0.97	
Some college	674	380 (56.4)	0.86	0.70–1.06	
≥ College degree	889	526 (59.2)	ref	-	

Bleeding and/or spotting episode: Bleeding/spotting days bounded on either end by 2 days of no bleeding or spotting.
N: number of participants in each category; n (%): number and percentage of women with any bleeding and/or spotting episodes in the first 4 cycles of contraceptive vaginal system use in each category.

Users of the SA/EE CVS experienced rates of unscheduled B/S comparable to other CHCs, except for the ENG/EE vaginal ring, which is associated with a lower incidence of unscheduled B/S [11,12,23–27]. This difference in unscheduled B/S between the ENG/EE vaginal ring and other CHCs, especially COCs, has been attributed to continuous release of contraceptive hormones in the vagina, without daily fluctuation typically found in COCs [12,25–27]. The SA/EE CVS also has a continuous release of hormones in the vagina, but the progestin released by the CVS differs from that released by the ENG/EE vaginal ring [28]. Endometrial bleeding patterns may differ in response to specific steroid receptor binding patterns of various progestins; however, the mechanism is unclear [29,30].

Knowing that women consider unscheduled bleeding a negative characteristic of CHC use [10,19], we examined the factors associated with having any episode of unscheduled B/S in the first 4 cycles of CVS use. Compared with White women, Black women, who represent 14% of the population in our study, were more likely (adjusted OR=1.5) to report any episode of unscheduled B/S in the first 4 cycles of CVS use. In most studies assessing the bleeding profile of ENG/EE vaginal ring users, White/Caucasian women have represented more than 90% of the sample [25–27], which could have affected the incidence of unscheduled B/S in these studies. Bleeding patterns among ENG-releasing implant users showed that women from Southeast Asia had a lower number of B/S days per reference period than those from the US and Europe/Chile [31]; however, the association between race or ethnicity and bleeding patterns has not been previously addressed among CHC users. We also found that women with fewer years of schooling were less likely to report any episode of unscheduled B/S in the first 4 cycles of CVS use. Previous studies of bleeding patterns and ENG/EE vaginal ring did not present data on educational level of the participants [12,25–27,32]. One explanation for our finding is reporting bias, with women of low educational status less likely to report an episode of unscheduled B/S episodes than women with higher education attainment. A randomized clinical trial comparing the data on bleeding patterns provided with text messages versus paper diaries in intrauterine contraceptive users found that women with fewer years of schooling had a higher rate of missing information, especially in paper diaries [33]. Further studies evaluating factors associated with unscheduled B/S episodes in CHC users will be necessary to establish whether demographic and other characteristics are associated with these episodes, which can enhance comparability among studies [10] and improve the counseling and management of unscheduled B/S by health care providers.

In conclusion, participants using the SA/EE CVS for up to 13 cycles experienced good cycle control that compares favorably to most other CHCs, with a low discontinuation rate due to unacceptable bleeding. Proper counseling on the expected bleeding profile with the use of the CVS may increase adherence and also help women to align their preferences with the contraceptive method's characteristics. With the recent regulatory approval of the SA/EE CVS by the FDA (Annovera®), the information on bleeding will be an important component of the information women receive about use of this novel contraceptive.

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