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# Segesterone acetate/ethinyl estradiol 12-month contraceptive vaginal system safety evaluation☆,☆☆

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ABSTRACT

*Objectives:* To evaluate safety outcomes from clinical studies of a 12-month contraceptive vaginal system (CVS) releasing an average of segesterone acetate (SA) 150 mcg and ethinyl estradiol (EE) 13 mcg daily.
*Study design:* We integrated clinical safety data from nine studies in which women used the CVS for 21 consecutive days and removed it for 7 days of each 28-day cycle. Four studies used the final manufactured CVS, including a 1-year pharmacokinetic study, two 1-year phase 3 trials and a second-year treatment extension study. We assessed safety by evaluating adverse events women reported in a daily diary. We also included data from focused safety studies evaluating endometrial biopsies, vaginal microbiology and liver proteins from one of the phase 3 studies.
*Results:* The combined studies included 3052 women; 2308 women [mean age 26.7±5.1 years; mean body mass index (BMI) 24.1±3.7 kg/m$^2$] received the final manufactured CVS, of whom 999 (43.3%) completed 13 cycles of use. Women using the final CVS most commonly reported adverse events of headache ($n$=601, 26%), nausea ($n$=420, 18%), vaginal discharge/vulvovaginal mycotic infection ($n$=242, 10%) and abdominal pain ($n$=225, 10%). Few (<1.5%) women discontinued for these complaints. Four (0.2%) women experienced venous thromboembolism (VTE), three of whom had risk factors for thrombosis [Factor V Leiden mutation ($n$=1); BMI>29 kg/m$^2$ ($n$=2)]. During 21,482 treatment cycles in the phase 3 studies evaluable for expulsion, women reported partial expulsions in 4259 (19.5%) cycles and complete expulsions in 1509 (7%) cycles, most frequently in the initial cycle [499/2050 (24.3%) and 190/2050 (9.3%), respectively]. Safety-focused studies revealed no safety concerns.
*Conclusion:* The 1-year SA/EE CVS has an acceptable safety profile. Additional studies are warranted in obese women at higher risk of VTE.

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*Implications:* This 1-year contraceptive vaginal system represents a new long-term, user-controlled and procedure-free option with a safety profile similar to other combination hormonal contraceptives. The same precautions currently used for combination hormonal contraceptive prescriptions apply to this new contraceptive vaginal system.


## 1. Introduction

Segesterone acetate (SA), also known as Nestorone®, is a novel 19-nor-progesterone that is inactive orally but highly effective when administered via implantable, vaginal and transdermal systems [1]. Like progesterone, SA binds specifically to progesterone receptors but not to androgen or estrogen receptors, thus limiting undesired androgen, antiandrogen or estrogenic effects [2]. Although SA binds to the glucocorticoid receptor, no glucocorticoid-related effects appear at therapeutic doses [2]. SA does not transactivate the androgen receptor, and its metabolites do not interact with the GABA-A receptor [3]. This latter finding could theoretically avoid mood changes and sleepiness described with progesterone treatment related to allopregnanolone (the main progesterone metabolite) action on the GABA-A receptor [3].

The Population Council developed an SA/ethinyl estradiol (EE) contraceptive ring with a final formulation delivering an average of SA 150 mcg and EE 13 mcg daily. The US Food and Drug Administration approved this product as a contraceptive vaginal system (CVS) in April 2018. Women used the CVS for 21 consecutive days and then removed it for 7 days in each 28-day cycle for all studies. Women can use the same CVS for up to 13 cycles (1 year). The CVS requires minimal to no daily attention and can be inserted or removed without a trained health provider. This report summarizes the safety data from two phase 3 studies and seven other clinical studies that included a broad range of women at United States (US) and non-US sites.

## 2. Methods

The overall safety evaluation plan for the SA/EE 150/13 CVS program included phase 1 and 2 studies of multiple doses of pilot formulations manufactured by the Population Council (New York, NY, USA) and two phase 3, 13-cycle studies (ClinicalTrials.gov as NCT00455156 and NCT00263341) with the final formulation manufactured by QPharma (Malmö, Sweden), a US-only study at 15 sites, and a multinational study at 12 US and non-US sites. The US-only study included three focused, safety substudies at specific sites, which assessed vaginal microbiology [4], endometrial changes and coagulation factor changes [5] in addition to the primary efficacy and safety endpoints. A drug–drug interaction study tested the effects of miconazole formulations on EE and SA vaginal absorption [6]; a pharmacokinetic (PK) study compared EE exposure between the pilot SA/EE 150/13 CVS and an approved levonorgestrel (LNG) 150 mcg/EE 30 mcg oral contraceptive during one cycle of use; and a 3-month, pharmacodynamic (PD), phase 1 study compared the impact of EE on hepatic proteins with oral versus vaginal delivery [7]. Finally, a 13-cycle, phase 2, dose-finding study of the pilot SA/EE 150/13 CVS evaluated vaginal and cervical epithelium by colposcopy [8,9]. The institutional review boards (IRBs) of the Population Council and one contracted by the National Institute of Child Health and Human Development's Contraceptive Clinical Trials Network Coordinating Center (Advarra, Columbia, MD 21046), and each participating site's IRB or Ethical Committee approved the protocols. All subjects signed written informed consent prior to initiating any study procedures.

The two phase 3, multicenter, single arm, open-label studies, conducted from 2006 to 2009, were identically designed and provided most of the safety information. Participants were healthy, sexually active, nonpregnant, nonsterilized women 18–40 years old. Subjects reported AEs, concomitant medications and CVS expulsions (partial or complete) on diary cards (see definitions in Supplemental Information). During the first 6 months of study enrollment, two venous thromboembolic events (VTEs) occurred in women who had a baseline body mass index (BMI) >29.0 kg/m$^2$ in the US-only study. The Data Safety Monitoring Board recommended limiting further enrollment to women with baseline BMI ≤29.0 kg/m$^2$ and to discontinue women in the two studies with BMI >29.0 kg/m$^2$. An additional open-label investigation collected PK and PD data from 39 subjects during cycles 1, 3 and 13 and safety data from all cycles of this study (see Supplemental Information). The safety data of this PK/PD study were part of each pooled dataset.

For the overall integrated safety summary analysis, we created three pooled datasets of SA/EE CVS use (Table 1). Investigators graded relatedness of AEs to CVS use as possibly, probably or definitely/highly probably (Supplemental Table 1S).

In a multicenter substudy of the US phase 3 study, investigators enrolled 156 women to evaluate endometrial safety of the SA/EE 150/13 CVS for 13 cycles. Subjects had a baseline endometrial biopsy between days 7 and 14 of the screening cycle for women not currently using combination hormonal contraceptives (CHCs) or at any time prior to initiating the CVS for women using CHCs. Investigators excluded women whose screening biopsies showed hyperplasia or other anomalies. The first 25 women had a second endometrial biopsy at cycle 6 (days 20–24), and the remaining women had a second biopsy at cycle 13 (days 20–24) or at early termination if enrolled for at least 3 months. Three blinded, independent, board-certified pathologists read each of the biopsies.

We performed all statistical analyses using SAS® version 9.2 or higher. We used descriptive statistics to summarize the safety variables.

**Table 1**
SA/EE CVS safety analysis studies

| Population/analysis set | Product studied | Doses studied (mcg/day) | Total subjects |
|---|---|---|---|
| All-dose SA/EE CVS | Phase 3[a] and Pilot SA/EE CVS | 50/10<br>50/20<br>150/13<br>150/20<br>200/13 | 2843 |
| All SA/EE 150/13[b] CVS | Phase 3[a] and Pilot SA/EE CVS | 150/13 | 2569 |
| Phase 3 trials SA/EE 150/13[b] CVS | Phase 3 SA/EE CVS[a] | 150/13 | 2308 |

The all-dose SA/EE CVS dataset ($n$=2843) and the SA/EE 150/13 CVS dataset ($n$=2569) are used as the denominator for program-wide SAE assessments, and the phase 3 trials SA/EE CVS dataset ($n$=2308) are used as the denominator for the pivotal trial AEs and laboratory assessments.

[a] Formulation intended for marketing.

[b] In vitro release data initially supported an average daily release of 150/15 mcg/day for SA and EE, respectively. Estimates from an ex vivo study indicate 150/13 mcg/day for SA and EE, respectively.

**Table 2**
Subject disposition in the phase 3 trials ($n$=2308) analysis set of women using the SA/EE CVS, and reasons for discontinuation

| Disposition | All-dose SA/EE CVS ($n$=2843) | Phase 3 SA/EE 150/13 CVS ($n$=2308) | Phase 3 SA/EE 150/13 CVS BMI subgroups | |
|---|---|---|---|---|
| | | | ≤29.0 kg/m$^2$ ($n$=2099) | >29.0 kg/m$^2$ ($n$=209) |
| Completed the study | 1761 (62) | 1332 (58)[a] | 1296 (62) | 36 (17) |
| Discontinued prematurely | 1082 (38) | 976 (42) | 803 (38) | 173 (83) |
| AE[b] | 328 (12) | 281 (12) | 267 (13) | 14 (7) |
| Withdrew consent | 228 (8) | 214 (9) | 191 (9) | 23 (11) |
| Lost to follow-up | 220 (8) | 197 (9) | 184 (9) | 13 (6) |
| Eligibility[c] | 147 (5) | 147 (6) | 31 (1) | 116 (56) |
| Pregnancy | 63 (2) | 54 (2) | 50 (2) | 4 (2) |
| Compliance | 62 (2) | 49 (2) | 47 (2) | 2 (<1) |
| Expulsions | 33 (1) | 33 (1) | 32 (2) | 1 (<1) |
| Other | 3 (<1) | 1 (<1) | 1 (<1) | 0 |

All data are presented as $n$ (%).
[a] A total of 1332 completed the study and 999 completed the 13 cycles of CVS use. Not all completers who were enrolled late in the study completed 1 year due to the expiration of the drug.
[b] Most common AEs leading to discontinuation: headache 30 (1.3%), nausea 28 (1.2%), vaginal discharge/vulvovaginal mycotic infection 30 (1.3%) and abdominal pain 30 (1.3%). Metrorrhagia/menorrhagia occurred in 7% of the subjects, and 1.7% discontinued for this reason ($n$=39).
[c] The data safety monitoring board recommended discontinuation of subjects with a BMI >29.0 kg/m$^2$ during the study.

## 3. Results

The all-dose SA/EE CVS dataset included 2843 women who used one of five SA/EE CVS doses for 1 to 13 cycles (Table 2). Among the 2308 women enrolled in the phase 3 trials, 1332 (58%) women completed the study, and 999 completed 13 cycles (1 year) of use (Table 2). Of the 976 (42%) subjects who discontinued early, the most common reasons were an adverse event (AE; $n$=281, 12%), withdrawal of consent ($n$=214, 9%) and loss to follow up ($n$=197, 9%). Among the 214 (9%) women who withdrew consent, personal reasons were the most common reason for discontinuation (22%–78% depending on country). The change in eligibility related to BMI resulted in 147 (6%) women discontinuing early. Overall, investigators enrolled 209 women with BMI >29.0 kg/m$^2$ of whom 36 (17.2%) completed 13 cycles. The disposition of subjects in the supportive analysis sets was generally similar.

For the 2308 women in the phase 3 analysis set, most were 20–29 years ($n$=1609, 70%); range for all was 18.1–40.8 years (Table 3). About two thirds ($n$=1584, 69%) had a BMI of 20.1 to 27.0 kg/m$^2$, and most ($n$=1638, 71%) were Caucasian (Table 3). Demographics for the all-dose dataset were similar.

### 3.1. Overview of AEs

In the phase 3 trial analysis set, 2016 women (87%) reported at least one AE; most were considered mild or moderate in severity. Table 4 summarizes the most common adverse reactions (treatment-related and treatment-emergent AEs; occurring in >2% of subjects). Overall, 1602 (69%) women experienced AEs considered related to CVS use. Table 2S summarizes all AEs based on BMI. Two hundred eighty-one women (12%) discontinued due to AEs (Table 2).

Among women in the all-dose dataset ($n$=2843), 51 (2%) women experienced 55 serious AEs (SAEs). Sixteen SAEs occurred in more than 1 subject, including 4 VTEs, 2 allergic reactions and 10 spontaneous abortions. In the phase 3 trials, 47 SAEs occurred in 43 (2%) subjects. Investigators assessed 15 of these SAEs as possibly or probably related to the CVS. No SAEs occurred in more than 1 subject among 209 SA-only CVS participants. In the all-dose CVS analysis set ($n$=2843), five subjects reported gallbladder disease; two were considered serious, and a third resulted in a cholecystectomy. No reported pregnancies resulted in fetal anomalies and no deaths occurred in any study.

### 3.2. Venous thromboembolic events

Four nonfatal VTEs occurred at US study sites during a total exposure of 2021 woman-years (WY); all four subjects recovered. These events included one pulmonary embolism, two deep vein thromboses and one cerebral venous thrombosis that occurred in cycles 2, 3, 6 and 7, respectively. Three of these cases occurred in women with risk factors for VTEs: two subjects had high baseline BMI (29.1 and 30.8 kg/m$^2$), and one 39-year-old woman had Factor V Leiden heterozygous mutation discovered after the event. The fourth case occurred in a 28-year-old woman with a BMI of 25.2 kg/m$^2$ who withdrew from the study before a clotting evaluation could be conducted. She reported smoking <10

**Table 3**
Demographics and baseline characteristics of SA/EE CVS users in clinical trials

| Characteristic | All-dose SA/EE CVS ($n$=2843) | Phase 3 trials SA/EE 150/13 CVS ($n$=2308) |
|---|---|---|
| Age (years) | 27.0±5.2 | 26.7±5.1 |
| Age category | | |
| 18–19 | 166 (6) | 144 (6) |
| 20–24 | 992 (35) | 852 (37) |
| 25–29 | 914 (32) | 757 (33) |
| 30–35 | 553 (19) | 393 (17) |
| ≥36 | 218 (8) | 162 (7) |
| Parity | | |
| 0 | 1670 (59) | 1478 (64) |
| ≥1 | 1173 (41) | 830 (36) |
| Region | | |
| USA | 1723 (61) | 1536 (67) |
| Europe | 411 (14) | 309 (13) |
| Non-USA and non-Europe | 709 (24.9) | 463 (20.1) |
| Weight (kg) | 64.5±11.0 | 64.3±10.6 |
| BMI (kg/m$^2$) | 24.3±3.9 | 24.1±3.74 |
| ≤20.0 | 317 (11) | 251 (11) |
| 0.1–25.0 | 1485 (52) | 1245 (54) |
| 25.1–27.0 | 414 (15) | 339 (15) |
| 27.1–29.0 | 320 (11) | 264 (11) |
| >29.0 | 307 (11) | 209 (9) |
| Race | | |
| Asian | 82 (3) | 82 (4) |
| African ancestry | 328 (12) | 328 (14) |
| Caucasian | 1670 (59) | 1638 (71) |
| Other | 250 (9) | 248 (11) |
| Unknown | 513 (18) | 12 (<1) |
| Ethnicity[a] | | |
| Hispanic or Latina | 701 (25) | 690 (30) |
| Not Hispanic or Latina | 1641 (58) | 1618 (70) |
| Unknown | 501 (18) | 0 |

All data are presented as $n$ (%) or mean ± standard deviation.
The analysis sets are defined in Table 1. The all SA/EE 150/13 CVS analysis set includes all subjects in the phase 3 trial analysis set and is a subset of the all-dose SA/EE CVS analysis set.
[a] Ethnicity was captured on the case report form (CRF) using the word "Latino" for phase 3 studies; only "not Hispanic" or "Hispanic" was captured on the CRF of phase 2 studies. Ethnicity was not captured for any other study.

**Table 4**
Adverse reactions[a] occurring in >2% of subjects: phase 3 trial SA/EE CVS analysis set ($n$=2308)

| Adverse reaction | Subjects, $n$ (%) |
|---|---|
| Any event | 1602 (69) |
| Headache | 601 (26) |
| Nausea | 420 (18) |
| Vaginal discharge | 242 (10) |
| Uterine spasm | 225 (10) |
| Vulvovaginal mycotic infection | 173 (7) |
| Metrorrhagia[b] | 160 (7) |
| Breast tenderness | 134 (6) |
| Vomiting | 108 (5) |
| Genital pruritus female | 92 (4) |
| Urinary tract infection | 92 (4) |
| Migraine | 77 (3) |
| Vaginal candidiasis | 70 (3) |
| Libido decreased | 69 (3) |
| Acne | 66 (3) |
| Mood swings | 60 (3) |
| Dizziness | 58 (3) |
| Dyspareunia | 56 (2) |
| Vulvovaginal discomfort | 56 (2) |
| Withdrawal bleed[c] | 56 (2) |
| Breast pain | 49 (2) |

Discontinuation rates for the common adverse reactions were as follows: headache including migraine $n$=30 (1.3%), vaginal discharge/vulvovaginal mycotic infections $n$=30 (1.3%), nausea/vomiting $n$=28 (1.2%) and metrorrhagia/menorrhagia $n$=39 (1.7%).

[a] Includes treatment-emergent AEs considered possibly, probably or definitely related to treatment.

[b] Metrorrhagia includes verbatim terms of irregular bleeding, irregular spotting, breakthrough bleeding, breakthrough spotting, spotting, frequent spotting and prolonged spotting.

[c] Withdrawal bleed includes verbatim terms of heavy bleeding with menses, bleeding very much, prolonged bleeding with menses and frequent bleeding with menses.

cigarettes daily. Among the 2308 women enrolled in a phase 3 study (US and international sites) with a BMI <29.0 kg/m$^2$, the VTE rate was 10.8/10,000 WY [95% confidence interval (CI), 8.9–13.1]. No VTEs occurred among the 1120 (48%) of subjects enrolled in non-US sites.

### 3.3. CVS expulsions

Of the 2308 women in the phase 3 studies, 2096 (90.8%) had evaluable diary responses for expulsion. Overall, 1107 of the 2096 (52.8%) subjects reported at least one complete (24.6%) or partial expulsion (44.0%) during CVS use. Users reported CVS expulsion most frequently in the first cycle of use. Among the 2050 women who documented expulsion during the first cycle, 190 (9.3%) and 499 (24.3%) experienced complete and partial expulsions, respectively. When including all 21,842 treatment cycles eligible for expulsion analysis, complete expulsion occurred in 1509 (7.0%) cycles and partial expulsion in 4259 (19.5%) cycles. Only 115 of the 2096 (5.5%) of women required a replacement system due to a lost CVS.

### 3.4. Clinical laboratory values

No changes in measured clinical laboratory values occurred from baseline to end of treatment in 57% to 80% of the women in the phase 3 studies. Minimal, but not clinically relevant, changes in blood urea nitrogen, creatinine, hemoglobin and lipids occurred in the remaining women. Of these, 13 (0.6%) subjects had elevations of a single liver function test above normal at baseline, 11 of which improved during CVS use. Fifteen (0.6%) other subjects developed nonclinically significant elevations during therapy for at least one liver function test; none resulted in discontinuation.

Subjects had a median change in total cholesterol from baseline to end of study of +0.23 mmol/L. Median changes from baseline to end of study were +0.16 mmol/L for high-density lipoprotein, 0 mmol/L for low-density lipoprotein and +0.15 mmol/L for triglycerides.

Mean hemoglobin and hematocrit values remained stable. The mean change in hemoglobin from baseline to end of study was −2.7±8.3 g/L.

### 3.5. Vital signs and physical exam

Most subjects had normal vital signs at both assessments (Table 5). At baseline among participants at non-US and US sites, mean weight was 62.2±9.2 kg and 65.4±11.0 kg, respectively, and mean BMI was 23.6±3.2 kg/m$^2$ and 24.4±4.0 kg/m$^2$, respectively. The mean change in BMI from baseline to end of treatment was 0.1±1.2 kg/m$^2$; mean weight change was 0.4±3.3 kg. While investigators did not report any clinically relevant weight changes, 35 women reported weight increase as an AE. Eight women reported hypertension as an AE, all verified by medical staff, and one of those discontinued. Investigators also reported no clinically relevant changes in physical exam data from baseline to study end.

### 3.6. Endometrium

Seven women with hyperplasia ($n$=2), endometritis ($n$=1) and polyps ($n$=4) at baseline were excluded. Eighty-three subjects had end-of-treatment, follow-up biopsies. No endometrial hyperplasia or carcinoma was found. Secretory and atrophic/inactive tissues were the most common diagnoses.

## 4. Discussion

Data collated from the SA/EE CVS clinical trials demonstrate a safety profile as expected for a CHC containing EE, with no unexpected safety signals. Headache and nausea were among the most common adverse reactions; these AEs are also commonly reported with other CHCs. A few cases of gallbladder disease, also known to occur with estrogen use, were not unexpected. Whereas mood disorders have been reported with CHC use at rates up to 24% [10], only 3% of CVS users complained of mood swings. Lastly, we noted no safety concerns in the standard laboratory chemistry, hematology, vital signs or physical examination findings.

Three other safety studies have been published on the CVS [4,6,8,9]. A 13-cycle, multicenter, randomized, dose-finding study of the pilot rings evaluated 150 healthy, reproductive-age women using cervical and vaginal colposcopic examinations at cycles 3 and 13, finding no safety concerns with any dose [8,9]. In addition, co-administration of miconazole suppositories with the CVS led to higher systemic exposure of both SA and EE, while a miconazole cream did not affect hormone levels [6]. Thus, women using the SA/EE CVS may be advised to use an oral or cream formulation of miconazole rather than a suppository to treat vaginal candidiasis. Lastly, a single-center, microbiology substudy did not find any increase in vaginal infection incidence or clinically significant change in vaginal flora with use of the SA/EE 150/13 CVS for up to 13 consecutive cycles [4]. Cultures of the used CVS and those from vaginal fluid had similar prevalence and concentrations of microorganisms [4].

**Table 5**
Change from baseline of vital signs data: SA/EE 150/13 CVS analysis set ($n$=2308)

| Vital signs | Baseline mean (SD) | Median change (min/max) |
|---|---|---|
| Diastolic BP (mmHg) | 68.7 (7.7) | 0.5 (−28/30[a]) |
| Systolic BP (mmHg) | 108.4 (10.1) | 1.0 (−37/40[a]) |
| Pulse (bpm) | 73.9 (10.3) | 2.0 (−42/47) |
| Weight (kg) | 64.3 (10.6) | 0.2 (−17[b]/17.7[c]) |
| BMI (kg/m$^2$) | 24.1 (3.7) | 0.09 (−6.6/6.6) |

BP, blood pressure; min, minimum; max, maximum.

[a] Eight subjects reported hypertension as an AE (verified by the staff), and four of them received short-term antihypertensive treatment. Only one of these discontinued for hypertension of 132/102.

[b] Three subjects reported weight decrease as an AE.

[c] Thirty-five subjects reported weight increase as an AE; nine of these discontinued for the weight increase of 4–10 kg, and 1 of these was discontinued for BMI >29.0.

Of note is the 9% withdrawal of consent rate among the phase 3 study participants. Although it may suggest some unreported AEs, the reasons for withdrawal of consent were mainly personal such as being no longer sexually active, relocation and desiring pregnancy. Nonetheless, this consent withdrawal rate is similar to the 6% to 9.3% reported in contemporary studies of combined oral contraceptives [11,12].

With any CHC containing EE, one of the most concerning SAEs is VTE. In our safety database of 2843 women who used the SA/EE CVS in clinical trials, we observed four cases of VTE. Since two of the four cases occurred in women with a BMI >29.0 kg/m$^2$, a high BMI may have contributed to VTE risk. Notably, the estimated VTE risk of 10.8/10,000 WY in women with BMI ≤29.0 kg/m$^2$ is similar to other vaginal and transdermal CHC products (3–12 cases per 10,000 WY) [13,14]. No VTEs occurred in the non-US subgroup, representing 48% of the total study population with a lower mean weight and BMI. Even though a trend for increased BMI has occurred over the recent decades and mostly in the US [15], many previous phase 3 trials of approved CHCs excluded women with BMI >29 kg/m$^2$. As a result of discontinuing enrollment of women with BMI >29.0 kg/m$^2$, the sample size of obese subjects completing 13 cycles was significantly reduced, thereby limiting the safety conclusions in this subgroup. We could not estimate the rate of VTEs among women with a BMI >29.0 kg/m$^2$ due to the small number of women in this group. No VTEs were observed in our studies of SA-only formulations including 1463 subjects with 1558 WY of exposure, suggesting no risk attribution to the progestin SA [16].

The benefit–risk balance for contraceptive steroids is generally positive with regard to VTE, particularly when compared with that of pregnancy [17]. Pregnancy increases the risk of VTE as much or more than CHCs as the overall incidence of pregnancy-associated VTE is 5 to 65 cases per 10,000 WY [17]. Data are conflicting between prospective, active surveillance studies reporting no difference in VTE risk among different CHC formulations [13] and observational and database studies suggesting an increase in VTE risk with some combinations [17]. This discrepancy may be explained by different study designs and the fact that some observational studies do not adjust for important risk factors such as overweight, family history of thrombosis and smoking. Indeed height, weight and obesity are independent risk factors for VTE, and this risk is further enhanced in obese women using CHCs [18].

Three safety studies evaluated the effect of the SA/EE CVS and of EE vaginal delivery on hepatic protein synthesis. In one substudy [5], we found that CVS use for up to 13 cycles slightly changed plasma factor VIII, fibrinogen and protein S from baseline, but all remained within the normal range. However, sex hormone binding globulin (SHBG) levels increased above the normal range by cycle 6. Women not using CHCs before the CVS had greater changes versus recent CHC users whose baseline values were already higher with previous EE exposure [5].

Some measured hemostasis variables and SHBG were affected differently between groups in a comparative, 3-month study of the SA/EE 150/13 CVS versus the LNG/EE 150/30 OC, most likely because of the difference in androgenicity of the progestins. SHBG increased more in SA/EE users than in LNG/EE users as LNG transactivates the androgen receptor while SA does not [3,19,20]; however, SHBG is not a VTE risk factor [21,22]. For eight coagulation parameters, including coagulation activity, prothrombin fragment 1+2 and D-dimer, mean values with the pilot SA/EE CVS and LNG/EE OC were within their normal reference ranges, except for factors VII-t and VIII, which were slightly elevated with the CVS [20].

A third, randomized, crossover, single-center study of 14 postmenopausal women observed no differences in angiotensinogen, SHBG or clotting factors between EE 15 mcg orally and an EE-only vaginal ring [7]. Thus, the effects of EE-containing CHCs on hemostatic variables and estrogen-sensitive liver proteins are largely related to EE, independent of delivery route, and precautions for all EE-containing oral contraceptives, including the CVS, should be the same.

In conclusion, we found the overall SA/EE CVS safety data to be within expectations based on established outcomes with existing CHCs, although data are limited for obese women. Women with known risk factors for VTE are at risk of thrombosis that may be enhanced by any EE-containing contraceptive. Given the safety profile reported here, the marketed product Annovera™ (TherapeuticsMD, Boca Raton, FL, USA) will have the same precautions as required for other EE-containing CHCs.

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