Systemic exogenous progestins with or without estrogens are associated with decreased rates of venous procedures for varicose veins

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ABSTRACT

Objectives: Risk factors for varicose veins (VVs) such as female sex, pregnancy, and obesity are high estrogen states, yet the role of systemic progestins with or without estrogens (SPEs) in VV management is not well characterized. This study investigates how SPE use affects rates of venous procedures for patients with VV.

Methods: The TriNetX database was queried for subjects with *International Classification of Diseases*, 10th edition, diagnoses of asymptomatic VV, chronic venous insufficiency, and complicated VV (inflammation or ulceration). Patients were divided into a control cohort with no subsequent SPE use, a progestin-only cohort, and a combined estrogen-progestin (CEP) cohort. Further stratification by VV symptomology and premenopausal status (age <40 years) was also performed. Cohorts were one:one propensity matched on known and theorized risk factors for VV including age, race, prior pregnancy, and body mass index. The outcomes of interest were deep vein thrombosis, pregnancy, stab phlebectomy, endovenous ablation, and sclerotherapy.

Results: Database query yielded 674,838 controls, 7597 CEP patients, and 13,758 progestin-only patients before matching. After propensity matching, compared with controls, the CEP cohort received fewer stab phlebectomies (relative risk [RR], 0.52; 95% confidence interval [CI], 0.42-0.64; $P < .001$), endovenous ablations (RR, 0.50; 95% CI, 0.43-0.59; $P < .001$) or any venous interventions (RR, 0.68; 95% CI, 0.61-0.76; $P < .001$), with no difference in sclerotherapy ($P = .12$). Similarly, the progestin-only cohort was less likely to receive stab phlebectomy (RR, 0.37; 95% CI, 0.31-0.43; $P < .001$), endovenous ablation (RR, 0.35; 95% CI, 0.31-0.40; $P < .001$), sclerotherapy (RR, 0.65; 95% CI, 0.56-0.75; $P < .001$), and any venous procedure (RR, 0.57; 95% CI, 0.52-0.62; $P < .001$). Compared with the progestin-only cohort, the CEP cohort had higher rates of sclerotherapy (RR, 1.38; 95% CI, 1.12-1.72; $P = .003$) and overall venous procedures (RR, 1.16; 95% CI, 1.00-1.34; $P = .048$). When possible, analysis stratified by symptomatic status and menopausal status revealed similar findings for subcohorts. Finally, the CEP cohort had lower risk of pregnancy than controls during the first 1200 days of observation, but subsequently had greater risk of pregnancy (RR, 1.38; 95% CI, 1.21-1.57; $P < .001$). Kaplan-Meier analysis showed that the rates of venous intervention were lower throughout the observation period.

Conclusions: This large, population-based cohort study demonstrated that, despite variable risk of deep vein thrombosis and pregnancy for estrogen-progestin and progestin-only treatment cohorts, both SPE formulations were associated with significantly fewer venous procedures for VVs than controls, with progestin-only cohorts undergoing the fewest procedures. This warrants further investigation into the role of SPE in VV disease progression and the utility of systemic progestins as an adjunct therapy for VVs. (J Vasc Surg Venous Lymphat Disord 2025;13:102235.)

Keywords: Varicose veins; Venous insufficiency; Phlebectomy; Endovenous ablation; Sclerotherapy; Women's health

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Varicose veins (VVs) have a lifetime prevalence of ≤50% and are responsible for $3 billion in health care spending annually worldwide.[1,2] Beyond the cosmetic importance of treating VVs, inadequately treated pathology can be painful and can lead to skin ulceration.[3,4] Risk factors for VVs such as female sex, pregnancy, and obesity are all high estrogen states, suggesting that sex hormones such as estrogen and progestin may contribute to the development and progression of venous pathology.[5]

Systemic progestins and/or estrogens (SPE) formulations can either be progestin-only or combined estrogen-progestin (CEP). The role of these medications in the progression of VVs has not been well-studied and is difficult to anticipate. On one hand, they increase

rates of circulating progestin and estrogen, increasing risk of venous pathology, whereas on the other hand, they may prevent pregnancy, a known risk factor for VVs. At the cellular level, sex hormones modulate venous inflammation and contribute to vascular remodeling, but the net effect on VVs is unclear.[6-8] This study aimed to assess how SPE use in patients with VVs affects the overall rates of venous procedures between controls with no SHC use, CEP users, and progestin-only users with both asymptomatic and complicated VVs.

ARTICLE HIGHLIGHTS

- **Type of Research**: Retrospective cohort study using the TriNetX database
- **Key Findings:** Among all women with a diagnosis of varicose veins, the 7206 taking combination estrogen-progestin and the 11,597 taking progestin-only received significantly fewer venous procedures compared with one:one matched controls (relative risk, 0.68; 95% confidence interval, 0.61-0.76 [$P < .0001$] and relative risk, 0.57, 95% confidence interval, 0.52-0.62 [$P < .0001$], respectively).
- **Take Home Message:** These findings invite collaboration with obstetrics and gynecology to explore the potential of exogenous estrogen and progestin as an adjunct treatment for varicose veins.

METHODS

The study used data from the TriNetX US Collaborative Network (Cambridge, MA), which granted access to data from approximately 112 million patients spanning 63 health care organizations in the United States, including patients with private insurance, Medicare/Medicaid, and no insurance. TriNetX automatically collects and reports data across a patient's entire electronic health record, including patient demographics, diagnoses, procedures, and medications. The TriNetX database has been used previously to conduct both epidemiological and clinical studies relating to vascular surgery and was chosen because it gave the study enormous statistical power, allowed all regions of the United States to be represented, and collected data on pregnancy and SPE use, which are critical to this study.[9-11] Databases specific to vascular surgery, such as the Vascular Quality Initiative, may lack data on pregnancy and SPE use because it is not routinely relevant to the vascular specialist. All patient data were deidentified before collection, use, and transmission; therefore, this study was exempt from institutional review board approval.

A retrospective cohort investigation was conducted between January 1, 2013, and December 31, 2023. Patients aged ≥18 years with *International Classification of Diseases*, 10th edition, diagnoses for chronic venous insufficiency, asymptomatic VVs, and VVs with complications (such as inflammation, ulceration, or unspecified complications) were identified (Supplementary Table, online only). This population was subdivided into treatment groups based on SPE use after VV diagnosis. This generated a control group without subsequent SPE use, a progestin-only treatment group, and a progestin-estrogen combined hormonal contraception (CEP) treatment group. An estrogen-only cohort was considered but ultimately not included in the investigation owing to a low sample size. The low sample size for estrogen-only therapy was probably because estrogen-only treatment is contraindicated in patients with an intact uterus owing to the risk of uterine cancer.[12] Patients in treatment groups with an unknown route of hormone administration, nonsystemic administration (eg, topical), or treatment with SPE for <3 continuous months were excluded. Patients who underwent venous procedures before a diagnosis of VV were also excluded. Patients with first-time SPE use following a venous intervention were assigned to the control cohort. To generate premenopausal cohorts, women aged >40 years or with a diagnosis of menopausal or perimenopausal disorders were excluded. This methodology is in line with prior TriNetX studies identifying premenopausal and postmenopausal patients.[13,14] To generate asymptomatic VV and complicated VV cohorts, patients were filtered by the appropriate *International Classification of Diseases*, 10th edition, code.

The diagnosis of chronic venous insufficiency, asymptomatic VVs, and complicated VVs served as the index event for the control cohort, and VV diagnosis and subsequent SPE therapy was the index event for treatment groups. Baseline characteristics reflected patient data before the index event, whereas outcomes, by definition, occurred after the index event. To mitigate variances in baseline characteristics across patient groups, propensity-score matching was used with greedy nearest-neighbor matching with a caliper of 0.1 pooled standard deviations. Matching covariates included age, race, systemic hormonal contraception use preceding the diagnosis of VVs, history of pregnancy, tobacco and alcohol consumption, prior deep vein thrombosis (DVT), and body mass index. These factors were selected for their known or theorized influence on the development and progression of VV.[5,15,16] Laboratory values for endogenous levels of estrogen and progestin were not criteria for matching owing to the rarity of these data for patients in all cohorts. Because TriNetX did not allow manual chart review, data on medication adherence, use of conservative therapy (compression stocking, weight loss, etc), or loss to follow-up after a recommendation for venous procedure could not be assessed.

The outcomes of interest were compared following propensity-matching. The primary outcomes included the proportion of patients who underwent stab phlebectomy, endovenous procedures (radiofrequency, laser,

and chemical adhesive), sclerotherapy, and any venous intervention (which counted a patient only once even if they underwent multiple types of procedures). Secondary outcomes of interest included rates of DVT and pregnancy (Supplementary Table, online only). Missing data on diagnoses, medications, and outcomes are reported not having said diagnosis, medication, or outcome and TriNetX does not report proportion of variables that are missing on the front end. Categorical and continuous variables were analyzed with χ^2 and independent-sample t tests, respectively, with $\alpha = 0.05$. All statistics, including propensity matching, were computed within the TriNetX platform, which uses integrated R, version 3.4.4 (The R Foundation for Statistical Computing, Vienna, Austria), and Python, version 3.6.5 (Python Software Foundation, Centrum voor Wiskunde en Informatica, Amsterdam, the Netherlands).

RESULTS

A database query yielded 674,838 controls with no SPE after VV diagnosis, 7597 patients with subsequent CEP, and 13,758 patients with subsequent progestin-only therapy after the application of inclusion and exclusion criteria (Fig 1). The mean follow-up time for the control, CEP, and progestin-only cohorts was 5.5, 6.5, and 6.1 years, respectively. Before propensity score matching, controls were significantly older than the CEP and progestin-only treatment groups (62.6 years vs 48.4 and 48.3 years, respectively; $P < .001$), White (73% vs 71% vs 67%; $P < .001$), and Hispanic (28% vs 25% vs 27%; $P < .001$). Progestin-only cohorts demonstrated significantly higher rates of prior DVT (8% vs 4% for controls; $P < .001$) and prior pregnancy (21% vs 3% for controls; $P < .001$). As expected, the CEP cohort was the most likely to have prior CEP use (31% vs 1% for controls; $P < .001$), and the progestin cohort was most likely to have prior progestin-only use (38% vs 4% for controls; $P < .001$). Rates of venous procedures before the index event for all cohorts approximated 0%. This ensured that patients in treatment groups did not receive venous procedures during the interval between a VV diagnosis and SPE initiation (Table I). These patterns were consistent when stratifying by VV complication status.

One:one propensity matching generated 7206 patients in the control and CEP cohorts and eliminated the statistically significant differences in age, sex, and relevant comorbidities that existed before matching (Table II). When considering all women with any VV diagnosis, there was no significant difference between rates of DVT. The CEP cohort had significantly higher rates of pregnancy (relative risk [RR], 1.38; 95% CI, 1.21-1.57; $P < .001$). The CEP cohort received fewer stab phlebectomies (RR, 0.52; 95% CI, 0.42-0.64; $P < .001$), endovenous ablations (RR, 0.50; 95% CI, 0.43-0.59; $P < .001$), or any venous intervention (RR, 0.48; 95% CI, 0.41-0.56; $P < .001$); there was no difference in rates of sclerotherapy (RR, 0.87; 95% CI, 0.74-1.04; $P = .12$). These trends were generally reproduced when stratifying cohorts by complicated

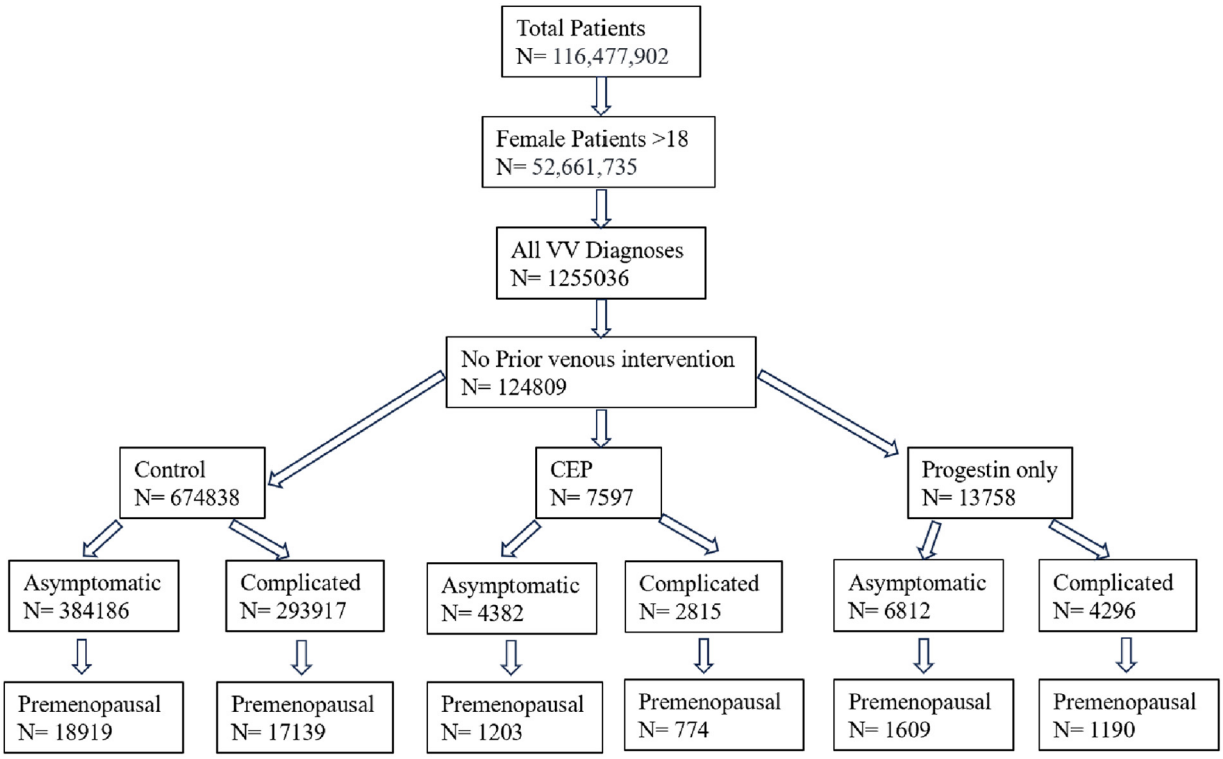

Fig 1. Cohort flowchart before propensity matching of any cohort or subcohort. *CEP*, Combined estrogen-progestin; *VV*, varicose veins.

Table I. Baseline characteristics for control, combined estrogen-progestin (*CEP*), and progestin-only cohorts containing all women with any varicose vein (VV) diagnosis before matching

Characteristic	Control	CEP	Progestin	*P* value
No.	674,838	7597	13,758	
Age, years	62.6 ± 16	48.4 ± 19	48.3 ± 17	<.0001
Race: White	73	71	67	.007
Black	13	12	18	<.0001
Asian	3	3	3	.272
Ethnicity: Hispanic	28	25	27	<.0001
DVT	4	5	8	<.0001
Prior pregnancy	3	14	21	<.0001
Tobacco use	3	6	5	<.0001
Alcohol use	2	3	4	<.0001
Prior progestin use	4	27	38	<.0001
Prior CEP use	1	31	7	<.0001
Prior stab phlebectomy	0	0	0	<.0001
Prior endovenous ablation	0	0	0	<.0001
BMI	31.6 ± 8.7	32.2 ± 9.6	33.5 ± 10.5	<.0001

BMI, Body mass index; *DVT,* deep vein thrombosis.
Values are number or mean ± 2 standard deviations.

VV and asymptomatic VV, and while restricting analysis to pre-menopausal females. One notable exception was that premenopausal women with any type of VVs had no significant difference in rates of stab phlebectomy compared with controls (RR, 0.66; 95% CI, 0.41-1.07; $P = .09$), but had significantly fewer venous procedures overall (RR, 0.54; 95% CI, 0.42-0.70; $P < .001$). Another exception was that asymptomatic VV patients on CEP were more likely to undergo sclerotherapy compared with controls (RR, 2.06; $P = .01$) (Table III).

Table II. Baseline characteristics of control vs combined estrogen-progestin (*CEP*) patients after 1:1 propensity matching

Characteristic	Control	CEP	*P* value
No.	7206	7206	
Age, years	44.5 ± 18.4	44.5 ± 18.6	.70
Race: White	70	70	.47
Black	12	12	.62
Asian	3	3	.86
Ethnicity: Hispanic	27	28	.30
DVT	3	3	.56
Prior pregnancy	14	14	.24
Tobacco use	3	3	.25
Alcohol use	2	2	.76
Prior progestin use	21	20	.11
Prior CEP use	31	32	.74
Prior stab phlebectomy	0	0	>.999
Prior endovenous ablation	0	0	>.999
Prior sclerotherapy	0	0	>.999
BMI, mean ± 2 SD	31.3 (8.7)	32.1 (9.8)	<.001

BMI, Body mass index; *DVT,* deep vein thrombosis; *SD,* standard deviation.
Values are number or mean ± SD.

Kaplan-Meier analysis demonstrated that women on CEP were more likely to remain pregnancy free than controls for the first 1500 days of observation. Past this period, this cohort had a greater probability of becoming pregnant (RR, 1.38 (1.21-1.57) ; $P < .001$). The CEP cohort was more likely to remain vascular intervention-free for the entirety of the observation period (Fig 2).

One:one propensity matching of control and progestin-only cohorts consisting of all female patients with any VV diagnosis resulted in cohorts of 11,597 each. The progestin-only patients were more likely to experience DVT than controls (RR, 1.16; 95% CI, 1.04-1.30; $P = .007$) and less likely to become pregnant (RR, 0.83; 95% CI, 0.74-0.93; $P = .001$). The progestin-only cohort was less likely to undergo stab phlebectomy (RR, 0.37; 95% CI, 0.31-0.43; $P < .001$), endovenous ablation (RR, 0.35; 95% CI, 0.31-0.40; $P < .001$), sclerotherapy (RR, 0.65; 95% CI, 0.56-0.75; $P < .001$), and any venous procedure (RR, 0.57; 95% CI, 0.52-0.62; $P < .001$). Further subdivision by symptomatic status of VVs and premenopausal status demonstrated no difference in DVT incidence between the cohorts, and no difference in incidence of pregnancy for women with complicated VV. Progestin cohorts maintained lower risk of venous procedures regardless of symptom status or menopausal status (Table IV).

Propensity matching progestin-only and CEP patients yielded 5549 women with any VV diagnosis in each

Table III. Outcomes for control vs combined estrogen-progestin (*CEP*) cohorts

Diagnosis	Subset (n)	Outcome	Control	CEP	RR (95% CI), *P* value
All VV	All (7206)	DVT	299 (4.1)	290 (4.0)	0.97 (0.82-1.13), .705
		Pregnancy	353 (4.9)	486 (6.7)	1.38 (1.21-1.57), <.001
		Stab phlebectomy	255 (3.5)	133 (1.8)	0.52 (0.42-0.64), <.0001
		Endovenous ablation	417 (5.8)	209 (2.9)	0.50 (0.43-0.59), <.0001
		Sclerotherapy	269 (3.7)	235 (3.3)	0.87 (0.74-1.04), .12
		Any intervention	689 (9.6)	470 (6.5)	0.68 (0.61-0.76), <.0001
	Premenopausal (1973)	DVT	41 (2.1)	27 (1.4)	0.66 (0.41-1.07), .086
		Pregnancy	271 (13.7)	328 (16.6)	1.21 (1.04-1.40), .011
		Stab phlebectomy	70 (3.5)	56 (2.8)	0.80 (0.57-1.13), .205
		Endovenous ablation	140 (7.1)	75 (3.8)	0.54 (0.41-0.70), <.0001
		Sclerotherapy	56 (2.8)	71 (3.6)	1.27 (0.90-1.79), .18
		Any intervention	194 (9.8)	153 (7.8)	0.79 (0.64-0.97), .02
Complicated VV	All (2715)	DVT	105 (3.9)	116 (4.3)	1.10 (0.85-1.43), .45
		Pregnancy	132 (4.9)	198 (7.3)	1.50 (1.21-1.85), .001
		Stab phlebectomy	201 (7.4)	95 (3.5)	0.47, (0.37-0.60), <.0001
		Endovenous ablation	331 (12.2)	147 (5.4)	0.44 (0.37-0.54), <.0001
		Sclerotherapy	204 (7.5)	183 (6.7)	0.90 (0.74-1.09), .27
		Any intervention	514 (18.9)	376 (13.8)	0.73 (0.65-0.83), <.0001
	Premenopausal (736)	DVT	14 (1.9)	N/A	N/A
		Pregnancy	100 (13.6)	128 (17.4)	1.28 (1.01-163), .0437
		Stab phlebectomy	48 (6.5)	43 (5.8)	0.90 (0.60-1.33), .588
		Endovenous ablation	85 (11.5)	57 (7.7)	0.67 (0.49-0.92), <.0001
		Sclerotherapy	44 (6.0)	54 (7.3)	1.22 (0.84-1.80), .30
		Any intervention	136 (18.5)	117 (15.9)	0.86 (0.69-1.08), .19
Asymptomatic VV	All (4166)	DVT	176 (4.2)	146 (3.5)	0.82 (0.67-1.03), .088
		Pregnancy	227 (5.4)	244 (5.9)	1.07 (0.90-1.28), .42
		Stab phlebectomy	N/A	N/A	N/A
		Endovenous ablation	22 (0.5)	N/A	N/A
		Sclerotherapy	18 (0.4)	37 (0.9)	2.06 (1.17-3.60), .01
		Any intervention	32 (0.8)	45 (1.1)	1.48 (0.90-2.21), .14
	Premenopausal (1151)	DVT	24 (2.0)	13 (1.1)	0.54, (0.28-1.06), .068
		Pregnancy	159 (13.8)	166 (14.4)	1.04 (0.85-1.28), .675
		Stab phlebectomy	N/A	0	N/A
		Endovenous ablation	N/A	N/A	N/A
		Sclerotherapy	N/A	N/A	N/A
		Any intervention	13 (1.1)	13 (1.1)	1.00 (0.47-2.15), >.999

CI, Confidence interval; *DVT,* deep venous thrombosis; *N/A,* not applicable; *RR,* relative risk; *VV,* varicose vein.
Any venous procedure includes either stab phlebectomy, endovenous ablation, or sclerotherapy.
Values are number (%) unless otherwise indicated.

cohort. Women on CEP were no more likely to have DVT (RR, 0.88; 95% CI, 0.74-1.04; $P = .139$), but were more likely to become pregnant (RR, 1.71; 95% CI, 145-2.01; $P < .001$). There was no significant difference in the rates of stab phlebectomy (RR, 0.92; 95% CI, 0.70-1.20; $P = .52$) or endovenous ablation (RR, 1.02; 95% CI,.81-1.27; $P = .86$). The CEP cohort was more likely to undergo sclerotherapy (RR, 1.38; 95% CI, 1.12-1.72; $P = .003$) and had more procedures overall (RR, 1.16; 95% CI, 1.00-1.34; $P = .048$). Among women with asymptomatic VV, CEP users were significantly less likely to have DVT (RR, 0.69; 95% CI, 0.55-0.88; $P = .003$). Differences in the rates of pregnancy and venous intervention were similar when restricting the analysis to asymptomatic or symptomatic VVs (Table V).

DISCUSSION

Both CEP therapy and progestin-only therapy were associated with decreased overall rates of venous procedures for VVs, with the progestin-only cohort having

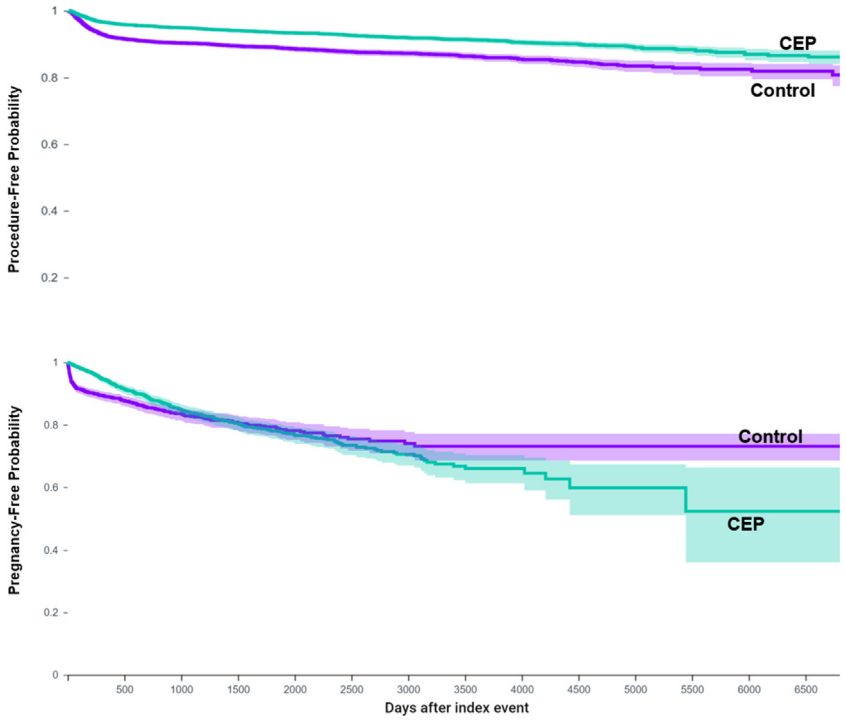

Fig 2. Kaplan-Meier analysis of procedure-free **(top)** and pregnancy-free **(bottom)** probability for the combined estrogen-progestin (*CEP*) **(blue)** and control **(purple)** cohorts. Colored shading represents the 95% confidence interval.

even lower rates of venous intervention than the CEP cohort. This finding suggests that, with respect to VVs, the potential effect of CEP use may outweigh the increased estrogen exposure and unexpected increased risk of pregnancy compared with controls. These findings were not restricted to only asymptomatic VV, but also complicated VVs, suggesting that SPE therapy was associated with fewer cosmetic and medically necessary procedures, and across all ages of adult women. This study represents the largest retrospective study investigating the association between SPE and venous procedures for VVs.

This observation has been previously described in a small case-control study, in which post-menopausal women on CEP had lower rates of venous ulceration compared with matched controls (odds ratio, 0.29).[17] A prior population-based study demonstrated that oral contraceptive use had a nonsignificant association with fewer VVs.[18] In assessing the reason for fewer procedures among SPE users, we consider prevention of pregnancy, socioeconomic differences between cohorts, and direct physiologic effects of hormonal contraception on lower-extremity veins.

Contraceptive effect. Pregnancy is a known risk factor for the development and progression of VVs, as the gravid uterus compresses the inferior vena cava, increasing pressures in the superficial venous system.[19] It would, therefore, follow that interventions that prevent pregnancy decrease the progression of VVs and need for intervention. As expected, CEP was protective from pregnancy for the first 3 years of observation. This observation verified that an appropriate treatment cohort was created in the TriNetX environment. The initial contraceptive benefit from CEP use supports the purely contraceptive mechanism of its effect on venous procedure rates. Past the 3-year point, women on CEPs had a greater rate of pregnancy than controls, likely owing to regular follow-up with gynecology, increasing the probability of a pregnancy being documented. Additionally, all three cohorts had an average age >40 years when including all women. Therefore, many women were likely prescribed SPE for noncontraceptive indications, such as endometriosis and vasomotor symptoms of menopause.[20,21] The combination of lower rates of venous procedures, despite higher rates of pregnancy over the long term, age of the cohorts, and low pregnancy rates (<7% in all cohorts), together indicate that contraception alone may not explain the association between SPE use and lower rates of venous procedures.

Socioeconomic considerations. Given that some insurance policies reject over 60% of claims for VV intervention, treatment can be cost prohibitive.[22] In fact, lower socioeconomic status (SES) is associated with more

Table IV. Outcomes for control vs progestin-only cohorts

Diagnosis	Subset (n)	Outcome	Control	Progestin only	RR (95% CI), *P* value
All VV	All (11597)	DVT	565 (4.9)	657 (5.7)	1.16 (1.04-1.30), .0069
		Pregnancy	625 (5.4)	518 (4.5)	0.83 (0.74-0.93), .0012
		Stab phlebectomy	547 (4.7)	200 (1.7)	0.37 (0.31-0.43), <.0001
		Endovenous ablation	817 (7.0)	287 (2.5)	0.35 (0.31-0.40), <.0001
		Sclerotherapy	432 (3.7)	281 (2.4)	0.65 (0.56-0.75), <.0001
		Any intervention	1158 (10.0)	655 (5.6)	0.57 (0.52-0.62), <.0001
	Premenopausal (2788)	DVT	73 (2.6)	94 (3.4)	1.29 (0.95-1.74), .099
		Pregnancy	418 (15.0)	337 (12.1)	0.81 (0.71-0.92), .0015
		Stab phlebectomy	129 (4.6)	60 (2.2)	0.47 (0.34-0.63), <.0001
		Endovenous ablation	197 (7.1)	77 (2.8)	0.39 (0.30-0.51), <.0001
		Sclerotherapy	94 (3.4)	57 (2.0)	0.61 (0.44-0.84), .003
		Any intervention	288 (10.3)	159 (5.7)	0.55 (0.46-0.67), .0001
Complicated VV	All (4741)	DVT	238 (5.0)	251 (5.3)	1.05 (0.89-1.25), .546
		Pregnancy	177 (3.7)	186 (3.9)	1.05 (0.86-1.29), .63
		Stab phlebectomy	405 (8.5)	144 (3.0)	0.36 (0.30-0.43), <.0001
		Endovenous ablation	680 (14.3)	207 (4.4)	0.30 (0.26-0.35) <.0001
		Sclerotherapy	368 (7.8)	238 (5.0)	0.65 (0.55-0.76), <.0001
		Any intervention	942 (19.9)	526 (11.1)	0.56 (0.51-0.62), <.0001
	Premenopausal (1147)	DVT	35 (3.1)	27 (2.4)	0.77 (0.47-1.27) .303
		Pregnancy	133 (11.6)	128 (11.2)	0.96 (0.77-1.21), .74
		Stab phlebectomy	109 (9.5)	44 (3.8)	0.40 (0.29-0.57), <.0001
		Endovenous ablation	167 (14.6)	59 (5.1)	0.35 (0.27-0.47) <.0001
		Sclerotherapy	77 (6.7)	48 (4.2)	0.62 (0.44-0.88), .008
		Any intervention	227 (19.8)	126 (11.0)	0.56 (0.45-0.68), <.0001
Asymptomatic VV	All (6469)	DVT	322 (5.0)	366 (5.7)	1.14 (0.98-1.32) .085
		Pregnancy	382 (5.9)	297 (4.6)	0.78 (0.67-0.90), <.0001
		Stab phlebectomy	N/A	N/A	N/A
		endovenous ablation	29 (0.4)	N/A	N/A
		Sclerotherapy	51 (0.8)	20 (0.3)	0.39 (0.23-0.66), .0004
		Any intervention	80 (1.2)	34 (0.5)	0.43 (0.28-0.63), <.0001
	Premenopausal (1571)	DVT	52 (3.3)	61 (3.9)	1.17 (0.82-1.69), .389
		Pregnancy	270 (17.2)	185 (11.8)	0.69 (0.58-0.82), <.0001
		Stab phlebectomy	N/A	N/A	N/A
		Endovenous ablation	N/A	N/A	N/A
		Sclerotherapy	N/A	N/A	N/A
		Any intervention	14 (0.9)	N/A	N/A

CI, Confidence interval; *DVT,* deep venous thrombosis; *N/A,* not applicable; *RR,* relative risk; *VV,* varicose vein.
Any venous procedure includes either stab phlebectomy, endovenous ablation, or sclerotherapy.
Values are number (%) unless otherwise indicated.

severe Clinical, Etiological, Anatomical, and Pathophysiological (CEAP) classification at initial patient presentation.[23,24] Patients from a lower SES are less likely to use family planning methods altogether, and specifically less likely to use oral contraceptives.[25] This factor theoretically makes the control population more likely to be economically disadvantaged. If SES were the predominant driver in the difference in rates of venous procedures, it would be expected that the control cohort would undergo fewer interventions, but this is the opposite of what was observed. Additionally, the results show similar findings for asymptomatic and complicated VVs. A complicated VV diagnosis requires skin ulceration and inflammation and is therefore CEAP class C4 or higher. Procedures for this class of venous disease are covered by Medicare or Medicaid without a trial of conservative treatment.[26] This fact decreases the likely likelihood of differences in procedures being driven by cost,

Table V. Outcomes for progestin-only vs combined estrogen-progestin (*CEP*)

Diagnosis (n)	Outcome	Progestin only	CEP	RR (95% CI), *P* value
All VV (5549)	DVT	261 (4.7)	229 (4.1)	0.88 (0.74-1.04), .139
	Pregnancy	216 (3.9)	369 (6.6)	1.71 (1.45-2.01), <.0001
	Stab phlebectomy	109 (2.0)	100 (1.8)	0.92 (0.70-1.20), .523
	Endovenous ablation	149 (2.7)	152 (2.7)	1.02 (0.81-1.27), .861
	Sclerotherapy	138 (2.5)	191 (3.4)	1.38 (1.12-1.72), .003
	Any intervention	316 (5.7)	366 (6.6)	1.16 (1.00-1.34), .048
Complicated VV (1969)	DVT	82 (4.2)	91 (4.6)	1.11 (0.83-1.49), .484
	Pregnancy	69 (3.5)	138 (7.0)	2.00 (1.51-2.65), <.0001
	Stab phlebectomy	62 (3.1)	67 (3.4)	1.08 (0.77-1.52), .654
	Endovenous ablation	87 (4.4)	107 (5.4)	1.23 (0.93-1.62), .141
	Sclerotherapy	94 (4.8)	127 (6.4)	1.35 (1.04-1.75), .02
	Any intervention	195 (9.9)	239 (12.1)	1.23 (1.03-1.47), .03
Asymptomatic VV (3126)	DVT	160 (5.1)	111 (3.6)	0.69 (0.55-0.88), .0025
	Pregnancy	121 (3.9)	178 (5.7)	1.47 (1.17-1.84), .0007
	Stab phlebectomy	N/A	N/A	N/A
	Endovenous ablation	N/A	N/A	N/A
	Sclerotherapy	N/A	28 (0.9)	N/A
	Any intervention	19 (0.6)	33 (1.1)	1.74 (0.99-3.05), .05

CI, Confidence interval; *DVT*, deep venous thrombosis; *N/A*, not applicable; *RR*, relative risk; *VV*, varicose vein.
Any venous procedure includes either stab phlebectomy, endovenous ablation, or sclerotherapy.
Values are number (%) unless otherwise indicated.

uninsurance, medical tourism, or loss to follow-up after conservative treatment.

Physiological effect. The relationship between estrogen, progesterone, and superficial and deep veins is complex. Retrospective clinical studies have demonstrated that higher serum levels of sex hormones and sex hormone binding globulins are associated with an increased risk of developing VVs.[27,28] Basic science studies have demonstrated that VVs have increased expressivity of estrogen and progesterone receptors compared with healthy vein.[29,30] Activation of both receptors modulates venous inflammation and remodeling, but neither hormone is clearly protective or pathological from an inflammatory or structural standpoint. Progestin may suppress inflammatory cytokines interleukin-6 and tumor necrosis factor-α, thereby reducing inflammation and increasing vascular tone.[31] However, progestin may also inhibit matrix metalloproteinase expression, which reduces extracellular matrix degradation and prevents necessary vascular remodeling.[32] Estrogen receptor activation may reduce inflammation by stabilizing endothelial function and may increase matrix metalloproteinase expression, allowing for extracellular matrix turnover and vascular remodeling.[33,34] Estrogen may also induce vasodilation via nitric oxide and prostacyclins, which may stabilize the vascular wall, but may also cause the venous dilation that promotes progression of disease.[35,36] Given this complexity, the basic science does not clearly account for the difference in rates of venous procedures between the control and SPE cohorts, nor the fewer procedures undergone by the progestin-only cohort compared with the CEP cohort. Rather, the association demonstrated in this study may provide some evidence that the net effect of SPE on venous pathology results in fewer procedures, albeit in the setting of the several limitations of this study discussed elsewhere in this article.

DVT risk. It has been well-established that SPE increases the risk of venous thromboembolism, which subsequently increases VV risk.[37,38] The lower observed incidence of DVT in the CEP cohort may be attributed to a variety of factors. CEPs are prescribed judiciously, particularly for individuals who exhibit known DVT risk factors such as prior DVT, hypercoagulable state, or smoking.[39,40] As a result, the patient population in the CEP group of this study carries a lower baseline thrombotic risk before CEP initiation. The addition of CEP may not increase thrombotic risk to a degree that supersedes the risk in the control group. Conversely, progestin users were more likely to experience DVT than controls, likely attributable to a higher baseline thrombotic risk, as seen in higher risk of DVT before VV diagnosis (8% progestins vs 5% controls). Although the study design does attempt to match for thrombotic risk by matching for DVT history, the full spectrum of hypercoagulable states, which includes malignancies and genetic conditions, cannot all be matched for. These patients with

a higher baseline risk for thrombosis are more likely to be prescribed progestin-only contraception and therefore demonstrate higher rates of DVT.

Limitations. This study has several limitations. It cannot account for the dosage, duration, or changes to systemic hormonal therapy because these data are unavailable in the TriNetX database. Additionally, although race was accounted for, some socioeconomic factors such as insurance status and home address were not available to perform a more robust investigation regarding how access to venous services may be influencing rates of venous procedures. Furthermore, metrics such as the vein location, length of lesion, and degree of venous reflux are unavailable in TriNetX, as is CEAP score for patients' venous disease. Therefore, this study is limited to analyzing procedural data. Fewer procedures do not equate to less progression of disease, because procedure rates may be affected by patient or provider preference, underinsurance, and medical tourism, especially for asymptomatic VV. Using institutional data to add these missing parameters is an opportunity for further research.

Systemic hormonal contraception brings with it thrombotic and metabolic risks that warrant careful evaluation. Therefore, this retrospective, population-based cohort study is not sufficient to advocate for the initiation of SPE in all patients with VVs. However, the data supports that women with VV who are already on SPE may continue it, because it may be a valuable adjunct to the procedural management of their condition.

CONCLUSIONS

This population-based retrospective cohort study demonstrated that both estrogen-progestin combination therapy and progestin-only therapy were associated with decreased rates of venous procedures for both asymptomatic and complicated VVs, possibly secondary to pregnancy prevention and the direct effect of therapy on VVs. This study is hypothesis generating and encourages further investigation of how systemic hormonal therapy affects VV progression. It also offers the opportunity for vascular surgeons to collaborate with colleagues in obstetrics/gynecology to further research the role exogenous progestins and estrogens may play in the future management of VVs.

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AUTHOR CONTRIBUTIONS

Conception and design: PJ, PD, BA
Analysis and interpretation: PJ, AO, PD, LE, MN, DS, BA
Data collection: PJ
Writing the article: PJ, AO, PD
Critical revision of the article: PJ, PD, LE, MN, DS, BA
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