

Hormonal Contraception Use is Common Among Patients with Inflammatory Bowel Diseases and an Elevated Risk of Deep Vein Thrombosis

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Background: Persons with inflammatory bowel disease (IBD) have an increased risk of venous thromboembolism. We sought to examine whether the self-report of hormonal contraception (HC), as a proxy for exposure to estrogen-based contraception, was less common for women with multiple risk factors for venous thromboembolism.

Methods: We examined the prevalence of personal use of hormonal birth control in a large internet-based cohort of patients with IBD. To determine whether HC was less common among patients with IBD with increased risk of thrombosis, we estimated unadjusted and adjusted prevalence ratios (PRs) for the use of HC.

Results: Thousand four hundred ninety-nine female survey respondents answered optional fertility questions and were included in the analysis. The prevalence of HC was 33.7% (95% CI, 30.6%–36.9%) among women with Crohn's disease and was 32.6% (95% CI, 28.6%–36.8%) for women with ulcerative colitis. Women with one risk factor for thrombosis were not significantly less likely to receive HC (PR = 0.91, 95% CI: 0.76–1.08; adjusted PR = 0.94, 95% CI: 0.80–1.11) compared with women without risk factors nor were women with 2 or more risk factors (PR = 1.10, 95% CI 0.56–1.28; adjusted PR = 1.10, 95% CI: 0.83–1.45). The use of an intrauterine device was also similar between women with and without risk factors for venous thromboembolism.

Conclusions: The prevalence of HC use in women with multiple risk factors was similar to that in women without risk factors, which represents an opportunity for prevention. Gastroenterologists should ask patients with IBD using HC about risk factors for thromboembolic disease to identify patients who may benefit from alternative contraception.

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BACKGROUND

Inflammatory bowel disease (IBD), ulcerative colitis (UC), and Crohn's disease (CD) are characterized by chronic remitting and relapsing bowel inflammation.¹ The choice of contraceptive methods in patients with IBD is more complex because of an increased thromboembolic risk with the use of oral contraceptives containing estrogen in IBD along with the elevated baseline risk of venous thromboembolism (VTE) in IBD.^{2,3} Although IBD diagnosis is not an absolute contraindication to estrogen-based contraception, patients with active disease

or additional risk factors may benefit from alternative methods of contraception.

The prevalence of estrogen-based contraception use among patients with IBD has been reported to range from 39% to 51%.^{4–7} Despite the widespread use of these medications, the well-described risks of VTE are rarely addressed by gastroenterologists during clinical visits with patients with IBD.⁸ Alternatives to estrogen-based contraception exist. Several forms of intrauterine devices (IUD) are marketed in the United States and are well tolerated, highly effective, and not associated with increased risk of thrombosis.^{9,10} Progesterone-only contraceptive pills, implants, and injectables also avoid exposure to exogenous estrogen.¹¹

IBD diagnosis is a moderate risk factor for VTE with a risk ratio of 1.96 in a recent meta-analysis.¹² The absolute rate of VTE in population studies of patients with IBD is estimated at 0.1% to 0.5% per year.^{13–18} Among patients with IBD, active disease has been reported as a strong risk factor for deep vein thrombosis (rate ratio 6.4).¹⁹ The effect of VTE risk factors among patients with IBD is unknown, and care should be taken in generalizing studies of the general population to patients with IBD. New users of corticosteroids in the general population may have as much as a 3-fold increase in risk for VTE.²⁰ Obesity is a dose-dependent risk factor for VTE with an estimated hazard ratio of 1.07 per SD or 2.14 for obese versus normal weight women.^{21,22} Current smoking confers a relatively small increase in risk of VTE, with a relative risk of 1.23 in a recent meta-analysis.²³ Age is also a strong risk factor for VTE. Although

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patients of 30 years of age have an estimated incidence rate of less than 0.1% per years, those older than 80 years have an estimated rate of more than 1%.²⁴ Other important risk factors include long-haul travel, the metabolic syndrome, and air pollution,²⁵ but these data were not available in this study.

We used the Crohn's and Colitis Foundation of America (CCFA) Partners cohort of patients with IBD to study the exposure to estrogen-based contraception, using hormonal contraception (HC) as a proxy. This large, Internet cohort provides statistical precision to examine the association of risk factors for VTE with the choice of contraceptive. We sought to describe the prevalence of various methods of contraception among women with IBD and to examine whether the use of HC was limited or the use of IUDs was increased among women with multiple risk factors for thromboembolism.

MATERIALS AND METHODS

CCFA Partners Cohort

CCFA Partners is an Internet-based cohort of patients with IBD.²⁷ Patients were recruited through CCFA email rosters, chapter events, and promotional activities beginning in June 2012.²⁸ Patients aged 18 years or older with self-reported IBD were eligible. Web

forms incorporated logic and range checks to minimize missing or erroneous data in real time. Respondents were queried about demographic information, disease phenotype, medication use, and health-related behaviors. An optional module included questions about contraception, menstrual and pregnancy history, and gestational outcomes. The Institutional Review Board at the University of North Carolina at Chapel Hill approved the study protocol.

We included patients for analysis with CD or UC who answered the optional fertility module of the baseline CCFA Partners survey. Patients with indeterminate colitis were excluded. Patients who reported not being sexually active or currently trying to conceive and women who had undergone menopause or were pregnant or breastfeeding women were excluded. Women over the age of 60 were excluded regardless of whether they reported menopause. Within the surveys, patients who endorsed using any method of birth control with their current sexual partner were presented a follow-up question in which they could select one or more of the following birth control methods: no sexual relations that could result in pregnancy, barrier methods, IUDs, HC, rhythm or natural family planning, sterilization operation, and withdrawal.

Statistical Methods

We performed descriptive statistics, stratified by IBD subtypes, including number and percent of categorical variables. The prevalence and method of birth control use was tabulated for

TABLE 1. Baseline Demographic Characteristics of 1340 Patients With UC or CD Who Responded to the Fertility Questions of the CCFA Partners Survey and Were Included for Analysis

Patient Characteristics	Ulcerative Colitis			Crohn's Disease		
	N	Percent	Total	N	Percent	Total
Age						
Under 25	62	12.3	503	142	17.0	837
25–34	187	37.2	503	306	36.6	837
35–44	162	32.2	503	255	30.5	837
45–55	92	18.3	503	134	15.9	837
BMI						
Underweight ($<18.5 \text{ kg/m}^2$)	27	5.5	493	52	6.3	828
Normal ($18.5\text{--}24.9 \text{ kg/m}^2$)	305	61.9	493	482	58.2	828
Overweight ($25.0\text{--}29.9 \text{ kg/m}^2$)	92	18.7	493	161	19.4	828
Obese ($\geq 30.0 \text{ kg/m}^2$)	69	14.0	493	133	16.1	828
Education						
No college	18	3.7	487	64	8.1	808
Some college or higher	469	96.3	487	744	91.9	808
Race						
White	425	89.5	475	737	93.6	787
Black	10	2.1	475	16	2.0	787
Other	40	8.4	475	34	4.3	787

BMI, body mass index.

TABLE 2. Baseline Clinical Characteristics of 1340 Patients With UC or CD Who Responded to the Fertility Questions of the CCFA Partners Survey and Were Included for Analysis

Patient Characteristics	Ulcerative Colitis			Crohn's Disease		
	N	Percent	Total	N	Percent	Total
Current pouch	49	9.8	502	19	2.3	829
Current ostomy	16	3.2	501	44	5.3	827
Current smoking	18	3.6	502	65	7.8	837
Any history of surgery	66	13.1	503	381	45.5	837
Any history of hospitalization	244	48.5	503	597	71.3	837
Currently has PCP	218	90.8	240	357	88.4	404
Setting of GI treatment:						
Academic center	33	14.8	223	65	16.8	387
Private center	160	71.7	223	266	68.7	387
Other	30	13.5	223	56	14.5	387
Current medication use:						
Aminosalicylates	343	68.2	503	271	32.4	837
Corticosteroids	78	15.5	503	131	15.7	837
Immunomodulators ^a	112	22.3	503	300	35.8	837
Biologics ^b	99	19.7	503	378	45.2	837

^aIncludes azathioprine, 6-mercaptopurine, cyclosporine, tacrolimus, and methotrexate.

^bIncludes TNF- α , integrin, and IL-12/23 targeted therapies.

GI, gastroenterologist; PCP, primary care physician.

all included subjects. We constructed 95% profile likelihood binomial CIs around point estimates of prevalence over zero and exact intervals around point estimates of prevalence of zero.^{29,30}

We used generalized linear models with targeted maximum likelihood estimation to estimate unadjusted and adjusted prevalence ratios (PRs) for hormonal birth control use depending on known risk factors for thromboembolism.³¹ Risk factors were chosen from established clinical risk factors for VTE that were available to this study, including current smoking, current use of corticosteroids, and obesity.²⁵ We also examined the effects of having active IBD, defined as simple clinical colitis activity index >2 or short CD activity index >150.^{32,33} We chose adjustment sets to limit open confounding paths based on the examination of directed acyclic graphs. These factors included age, current smoking, IBD type, any history of surgery, and any history of hospitalization. Potential confounders were parameterized using flexible trend analysis and comparison of nested models based on Akaike information criterion corrected to minimize residual confounding. Age was parameterized as a restricted quadratic spline with internal knots at 25, 35, and 45 years. Because the outcome was much less common than the exposure, inverse probability of treatment weighting was used to control confounding in analysis of IUD use.³⁴ The exposure model was constructed using similar criteria to those of the HC analysis, including flexible trend analysis and comparison of nested models on Akaike information criterion corrected.

We performed a sensitivity analysis to examine the effect of outcome misclassification given that some patients with IBD endorsing HC use were likely using progesterone-only methods

(see Table 1, Supplemental Digital Content 1, <http://links.lww.com/IBD/B270>). In random imputation analyses, a proportion of patients with HC use were imputed to nonuse both randomly and assuming an association with exposure to risk factors. For this sensitivity analysis, bootstrap 95% confidence limits were calculated using 500 samples per estimate. Statistical analyses were performed in R 3.2.2.³⁵

RESULTS

Of 3402 women responding to the CCFA Partners baseline survey, 1538 answered the fertility questions and 1340 who were at risk for using contraception were included for analysis. The analytic cohort was young, predominantly white, and well educated (Table 1). Most patients received gastroenterology specialist care in a private center (Table 2). The use of birth control was common among women in all age groups (Table 3). HC was the most common method among 18- to 34-year-olds, a group that also frequently used barrier methods (Fig. 1). Surgical sterilization was more common in older age groups. Overall, a large proportion of women with IBD were exposed to HC. The prevalence among women with CD was 33.7% (95% CI 30.5%–36.9%) and those with UC was 32.6% (95% CI 28.6%–36.8%). IUD use was much less common with a prevalence of 6.3% (95% CI 4.8%–8.1%) among patients with CD and 7.0% (95% CI 5.0%–9.4%) among patients with UC.

Female patients with IBD who had multiple risk factors for thromboembolism had similar overall prevalence of HC use to women with no risk factors (Table 4). Patients who were

TABLE 3. Prevalence and 95% Confidence Limits (CL) of Birth Control Use Among 1340 Responding Patients With CD and UC

	Ages 18–34		Ages 35–44		Ages 45–55	
	Prevalence, %	95% CL	Prevalence, %	95% CL	Prevalence, %	95% CL
Any method—CD	73.7	69.5–77.6	72.2	66.5–77.4	56.0	47.5–64.2
Abstinence	6.0	4.1–8.5	7.1	4.3–10.6	2.2	0.6–5.7
Barrier method	28.6	24.5–32.9	15.3	11.2–20.0	4.5	1.8–8.9
IUD	6.5	4.4–9.0	8.2	5.3–12.0	2.2	0.6–5.7
Hormonal method	46.0	41.4–50.6	22.7	17.9–28.1	13.4	8.4–19.9
Menstrual timing	2.2	1.1–3.9	2.0	0.7–4.2	3.0	0.9–6.8
Surgical sterilization	3.3	1.9–5.3	22.7	17.9–28.1	28.4	21.2–36.3
Withdrawal	13.6	10.7–17.0	3.5	1.7–6.3	3.7	1.4–7.8
Any method—UC	73.9	68.2–79.1	72.2	65.0–78.7	60.9	50.7–70.4
Abstinence	6.4	3.8–9.9	3.7	1.5–7.4	4.3	1.4–9.8
Barrier method	29.3	23.9–35.2	11.7	7.4–17.3	13.0	7.2–20.9
IUD	6.4	3.8–9.9	8.6	5.0–13.6	5.4	2.0–11.3
Hormonal method	45.8	39.7–52.0	22.8	16.8–29.7	14.1	8.0–22.2
Menstrual timing	0.0	0.0–1.5	3.7	1.5–7.4	2.2	0.4–6.6
Surgical sterilization	2.0	0.7–4.3	21.6	15.7–28.4	23.9	16.0–33.3
Withdrawal	10.4	7.1–14.6	4.3	1.9–8.2	5.4	2.0–11.3

underweight (adjusted PR = 0.62, 95% CI: 0.45–0.86), overweight (adjusted PR = 0.81, 95% CI 0.67–0.97), or obese (adjusted PR = 0.88, 95% CI: 0.73–1.05) had a lower prevalence of exposure to HC compared with women of normal weight. The negative associations with overweight and obesity were attenuated by adjustment, whereas the negative association with underweight was strengthened by adjustment. Exposure to HC use did not significantly differ between women receiving gastroenterology care in private versus academic settings (adjusted PR = 1.05, 95% CI: 0.83–1.33). Compared with women with no risk factors for thrombosis, women with one risk factor for thrombosis were not significantly less likely to receive HC (unadjusted PR = 0.91, 95% CI: 0.76–1.08; adjusted PR = 0.94, 95% CI: 0.76–1.08) nor were women with 2 or more risk factors (unadjusted PR = 1.10, 95% CI: 0.56–1.28; adjusted PR = 1.10, 95% CI: 0.83–1.45). In a sensitivity analysis examining the effect of outcome misclassification, estimates of the unadjusted PR for one or multiple risk factors for VTE were reduced if the use of nonestrogen HC was strongly associated with risk factors (see Table S-1, Supplemental Digital Content 1, Table S). In the analysis assuming the strongest potential for bias (15% of women using nonestrogen hormonal

contraception and those with any VTE risk factors being twice as likely to use the nonestrogen HC), the estimated prevalence of estrogen-containing contraception was estimated to be 31% to 34% lower than for women without VTE risk factors. Women with one or more risk factors for thrombosis were not significantly more likely to receive an IUD (unstandardized PR = 0.98, 95% CI: 0.95–1.01; standardized PR = 0.99, 95% CI: 0.95–1.03; Fig. 2).

DISCUSSION

In women with IBD who belong to a large Internet cohort, the use of HC was widespread (CD prevalence = 33.7, UC prevalence = 32.6%). We did not find evidence that HC use was less common among women with risk factors for thrombosis. To the contrary, point estimates of the PR were close to null. The absence of such a finding despite good statistical precision speaks to an opportunity for prevention because rates of thromboembolism are elevated among patients with IBD compared with the general population. Practice guidelines suggest that HC containing estrogen should be avoided even in healthy patients with multiple risk factors for thrombosis or atherosclerotic disease.^{36–38} There was

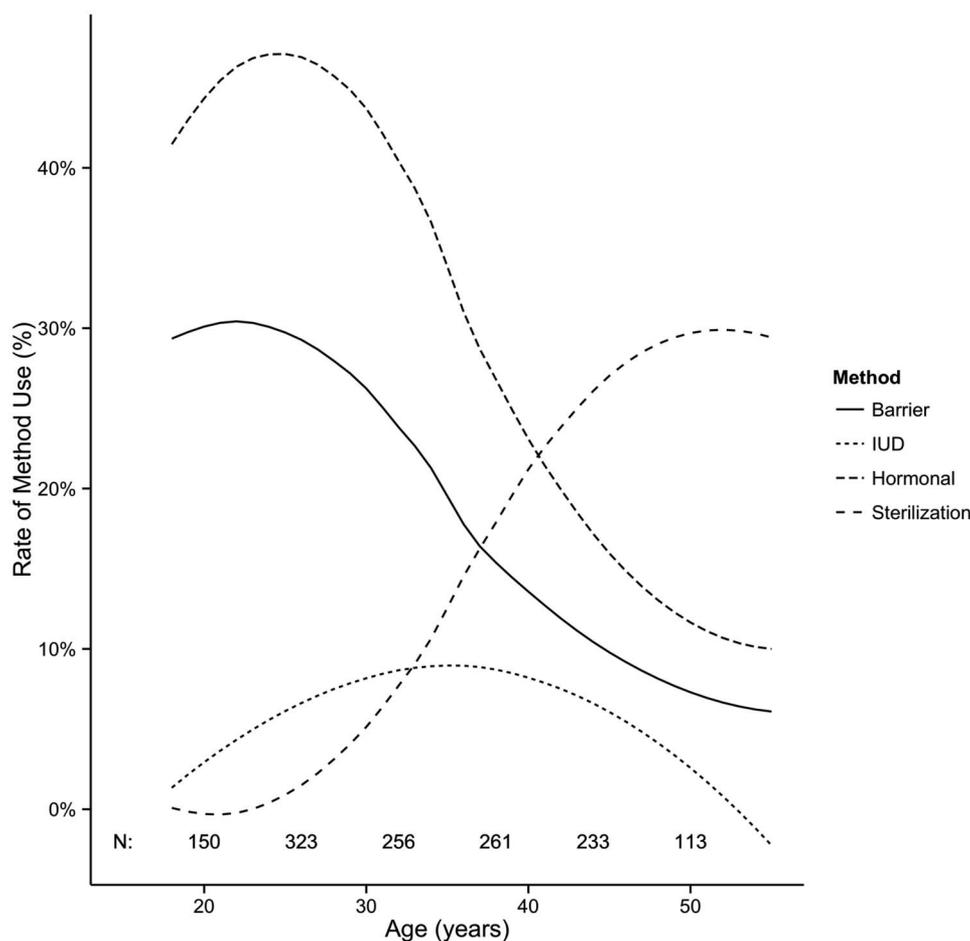


FIGURE 1. Trends in birth control methods by the age of respondent among 1340 women with UC or CD among patients at risk for using contraception.

TABLE 4. Adjusted and Unadjusted PRs and 95% CIs for HC in Women With IBD Who Answered Fertility Questions and Were at Risk^a as a Function of the Number of Established Risk Factors for Deep Vein Thrombosis

Patient Characteristic	N	Total	Unadjusted		Adjusted	
			PR	95% CL	PR	95% CL
Current active disease ^{b,c}	543	1197	1.00	0.86–1.17	0.96	0.82–1.12
Current corticosteroid use	209	1339	0.96	0.77–1.18	0.93	0.75–1.15
Current smoking ^d	83	1339	1.02	0.72–1.35	1.17	0.89–1.53
Body mass index, kg/m ²						
Normal ^c	786	1323	1.00	ref.	1.00	ref.
Underweight	79	1320	0.83	0.57–1.14	0.62	0.45–0.86
Overweight	253	1320	0.80	0.64–0.98	0.81	0.67–0.97
Obese	202	1320	0.77	0.60–0.97	0.88	0.73–1.05
No risk factors for thrombosis ^{c,e}	904	1339	1.00	ref.	1.00	ref.
One risk factor for thrombosis	379	1339	0.91	0.76–1.08	0.94	0.80–1.11
Two or more risk factors for thrombosis	56	1339	0.89	0.56–1.28	1.10	0.83–1.45

^aAt risk for HC was defined as being sexually active, not pregnant or breastfeeding, premenopausal, and not trying to conceive.

^bActive disease is defined as Simplified CD Activity Index ≥ 150 or Simple Clinical Colitis Activity Index ≥ 2 .

^cAdjusted for age, current smoking, CD versus UC, previous surgery, and previous hospitalization.

^dAdjusted for age, CD versus UC, previous surgery, and previous hospitalization.

^eRisk factors included corticosteroid use, smoking, and obesity.

a similar absence of evidence that IUD use was more common among women with risk factors for thrombosis.

The burden of thromboembolic disease among patients with IBD is substantial, with a recent meta-analysis reporting a risk ratio of 1.96 compared with the general population.¹² Reports of the rate of deep vein thrombosis in population-based studies suggest an incidence rate of 1 to 5 per 1000 person-years.^{13–18} Beyond the concern for VTE in general, mesenteric vein thrombosis is increasingly recognized as clinically significant among patients with IBD, particularly those with a history of surgery.^{39,40} Patients with IBD experience VTE at a younger age and with greater mortality than the general population.^{41,42}

Our findings are generally consistent with the previous literature in that women with IBD in this study used contraception at a higher rate than in the general population.⁴³ In a study with a mean age of 28 years, the reported rate was 40.5%.⁴ In a study with a mean age of 32 years, the rate of oral contraception use was 51%.⁴⁴ A study set in Cape Town, South Africa, reported a rate of 38.6% at a mean age of 31 years, but comparison may be limited by cultural differences.⁷ These studies of patients with IBD reported much higher usage than that reported in the National Survey of Family Growth, which reported 22.2% use among women aged 15 to 24 years, 16.9% among women aged 25 to 34 years, and 9.7% among women aged 35 to 44 years.⁴⁵ Studies have suggested that these differences could reflect the desire for “voluntary childlessness” among patients with IBD, but direct comparisons to national data are problematic because study populations with IBD differ from the general population in demographics and other characteristics.

Women in this study, with recruitment from June 2012 to the present day, were more likely to use IUDs than in the National

Survey of Family Growth from 2011 to 2013. This difference may reflect the young, highly educated women in this study. This may also represent progress toward lower risk or more effective contraceptives among this population. Further studies of the costs, risks, and benefits of contraception in patients with IBD are warranted given the prevalence of this exposure and the potential to avert serious adverse events in the high-risk population of patients with IBD.

Patients and clinicians face multiple challenges in the choice of family planning strategy in IBD. There is some evidence that HC can increase the risk of relapse among women already diagnosed with CD, although the data are conflicting.^{4,5,46} HC may alleviate symptoms related to the menstrual cycle in some women with IBD.⁴⁷ Despite this, patients with 2 or more risk factors for thromboembolism in addition to IBD would need significant benefits from estrogen-based methods as compared with other methods to justify the increased risk for thrombosis. Although it is unlikely that physicians treating IBD would place an IUD themselves, they have an important role in referring patients with multiple risk factors for IBD to a physician with expertise in contraception who could place an IUD or choose a satisfactory alternative method.

The study has several important strengths. The large sample size allows for statistically precise estimation of the prevalence of birth control methods across age, IBD type, and sex. Minimal missing data reduce the possibility of bias from systematic missing data. The Internet cohort design provides a large sample size with less missing data than postal methods.^{48,49} This study also has several limitations. As with any survey, there is a potential for selection bias. This cohort likely represents a better educated,

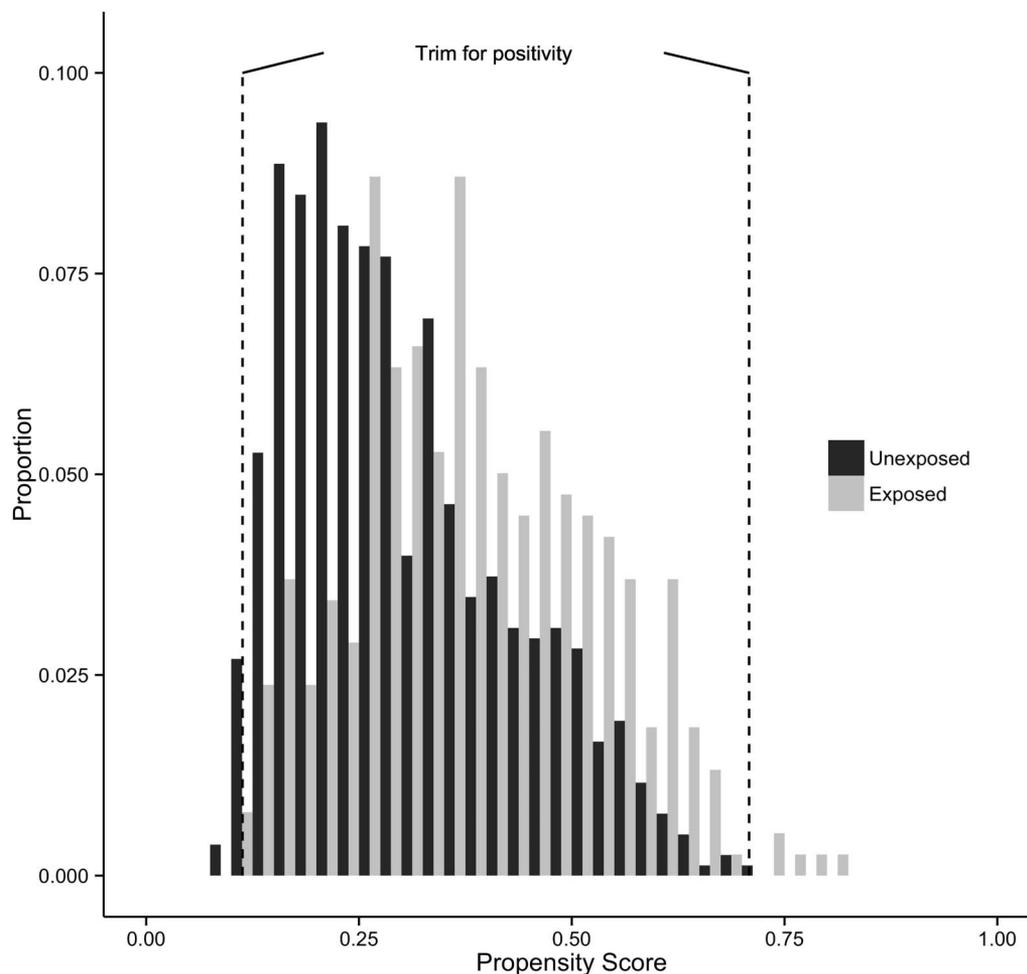


FIGURE 2. Distribution of propensity scores by the exposure, having one or more risk factors for deep vein thrombosis compared to having no risk factors.

English-speaking, and younger population of Internet users as compared with the general population.^{50,51} Our analysis of the number of additional risk factors among patients with IBD assumes that the impact of each risk factor on decision-making is equal and additive. This does not capture the complex reality of clinical decision-making or reflect the varying magnitude of risk factors. Nonetheless, this imperfect model has the utility to show that clinicians and patients in general do not seem to avoid estrogen-based contraception to the degree that might be expected in patients with risk factors for VTE.

A further limitation is that we did not ask about the use of specific hormonal contraceptives. Hormonal contraceptives vary in their thromboembolic risk depending primarily on estrogen content.^{52,53} Progesterone-only contraceptives are likely neutral with respect to thromboembolism, with a recent meta-analysis reporting a combined risk ratio of 1.03 (95% CI 0.76–1.39).¹¹ For combined oral contraceptives, the meta-analytic risk ratio of VTE varies widely ranging from 1.33 (95% CI 1.08–1.63) in one meta-analysis to 3.5 (95% CI 2.9–4.3) in another.^{54–57} We

evaluated the potential for bias due to the imperfect ascertainment of exposure to estrogen-based contraception. The use of progesterone-only contraceptive pills is uncommon at 0.4%, but progesterone-only implants or patches accounted for 4.2% of the National Survey of Family Growth respondents and Depo-Provera accounted for 10.6%.^{58,59} This suggests outcome misclassification could be as high as 15%. However, even with our most extreme hypothetical sensitivity assumptions, our data suggest that the use of estrogen-containing contraception is common in patients with IBD with VTE risk factors. The similar prevalence of IUD use between those with VTE risk factors and those without further supports our primary findings that there is very little avoidance of estrogen-containing HC in patients with IBD.

In summary, women in an Internet cohort of subjects with IBD reported using HC, a proxy for estrogen-based contraception, at rates greater than the general population. The use of HC among women with IBD was not limited in subjects with multiple additional risk factors for thrombosis. Although IBD diagnosis is not an absolute contraindication to estrogen-based

contraception, patients with active disease or additional risk factors may benefit from alternative methods of contraception. Gastroenterologists and primary care providers should counsel patients with IBD on the risk of thrombosis associated with HC use and make an informed decision based on patients' risk factors and preferences.

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