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

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### Abstract

**Background**—Persons with inflammatory bowel disease (IBD) have an increased risk of venous thromboembolism (VTE). We sought to examine whether 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 VTE.

**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 IBD patients with increased risk of thrombosis, we estimated unadjusted and adjusted prevalence ratios (PR and aPR) for use of HC.

**Results**—1,499 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 hormonal contraception (PR = 0.91, 95% CI 0.76 – 1.08; aPR = 0.94, 95% CI 0.80 – 1.11) compared to women without risk factors, nor were women with two or more risk factors (PR = 1.10, 95% CI 0.56 – 1.28; aPR = 1.10, 95% CI 0.83 – 1.45). Use of an intrauterine device was also similar between women with and without risk factors for VTE.

**Conclusion**—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 IBD patients using HC about risk factors for thromboembolic disease to identify patients who may benefit from alternative contraception.

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## Background

The inflammatory bowel diseases (IBD), ulcerative colitis (UC) and Crohn's disease (CD), are characterized by chronic remitting and relapsing bowel inflammation.<sup>1</sup> The choice of contraceptive methods in patients with IBD is more complex because of an increased thromboembolic risk with use of oral contraceptives containing estrogen in IBD along with the elevated baseline risk of venous thromboembolism (VTE) in IBD.<sup>2, 3</sup> Though 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%<sup>17-20</sup> Despite the widespread use of these medications, the well-described risks of VTE are rarely addressed by gastroenterologists during clinic visits with IBD patients.<sup>21</sup> Alternatives to estrogen-based contraception exist. Several forms of IUD are marketed in the United States and are well tolerated, highly effective, and not associated with increased risk for thrombosis.<sup>22, 23</sup> Progesterone-only contraceptive pills, implants, and injectables also avoid exposure to exogenous estrogen.<sup>24</sup>

IBD diagnosis is a moderate risk factor for VTE with a risk ratio of 1.96 in a recent meta-analysis.<sup>4</sup> The absolute rate of VTE in population studies of patients with IBD is estimated at 0.1 – 0.5% per year.<sup>5-10</sup> Among patients with IBD, active disease has been reported as a strong risk factor for deep vein thrombosis (rate ratio 6.4).<sup>25</sup> 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 threefold increase in risk for VTE.<sup>11</sup> Obesity is a dose-dependent risk factor for VTE with an estimated hazard ratio of 1.07 per standard deviation or 2.14 for obese versus normal weight women.<sup>12, 13</sup> Current smoking confers a relatively small increase in risk for VTE, with a relative risk of 1.23 in a recent meta-analysis.<sup>26</sup> Age is also a strong risk factor for VTE. While patients of 30 years of age have an estimated incidence rate less than 0.1% per years, those over 80 years of age have an estimated rate over 1%.<sup>14</sup> Other important risk factors include long-haul travel, the metabolic syndrome, and air pollution,<sup>15</sup> but these data were not available in the present study.

We used The Crohn's and Colitis Foundation of America (CCFA) Partners Cohort of patients with IBD to study 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 IUD was increased among women with multiple risk factors for thromboembolism.

## Materials and Methods

### The Crohn's and Colitis Foundation of America (CCFA) Partners Cohort

CCFA Partners is an Internet-based cohort of patients with inflammatory bowel diseases.<sup>27</sup> Patients were recruited through Crohn's and Colitis Foundation of America (CCFA) email rosters, chapter events, and promotional activities beginning in June 2012.<sup>28</sup> Patients age 18 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 age 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, IUD, hormonal contraception, rhythm or natural family planning, sterilization operation, and withdrawal.

### Statistical Methods

We performed descriptive statistics, stratified by IBD subtype, including number and percent for categorical variables. The prevalence and method of birth control use was tabulated for all included subjects. We constructed 95% profile likelihood binomial confidence intervals (CI) around point estimates of prevalence over zero, and exact intervals around point estimates of prevalence of zero.<sup>29, 30</sup>

We used generalized linear models with targeted maximum likelihood estimation to estimate unadjusted and adjusted prevalence ratios (PR) for hormonal birth control use depending on known risk factors for thromboembolism.<sup>31</sup> Risk factors were chosen from established clinical risk factors for VTE that were available to the present study, including current smoking, current use of corticosteroids, and obesity.<sup>15</sup> We also examined the effects of having active IBD; defined as simple clinical colitis activity index >2 or short Crohn's disease activity index >150.<sup>32, 33</sup> We chose adjustment sets to limit open confounding paths based on 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 (AICc) 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.<sup>34</sup> The exposure model was constructed using similar criteria to the hormonal contraception analysis, including flexible trend analysis and comparison of nested models on AICc.

We performed a sensitivity analysis to examine the effect of outcome misclassification given that some patients with IBD endorsing hormonal contraception use were likely using progesterone-only methods. In random imputation analyses, a proportion of patients with hormonal contraception use were imputed to non-use 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.<sup>35</sup>

## Results

Of 3,402 women responding to the CCFA Partners baseline survey, 1,538 answered the fertility questions and 1,340 who were at risk for using contraception were included for analysis. The analytic cohort was young, predominantly Caucasian, and well educated (table 1). Most patients received GI specialist care in a private center (table 2). Use of birth control was common among women in all age groups (table 3). Hormonal contraception was the most common method among 18 to 34 year olds, a group that also frequently used barrier methods (figure 1). Surgical sterilization was more common in older age groups. Overall a large proportion of women with IBD were exposed to hormonal contraception. The prevalence among women with CD was 33.7% (95% CI 30.5 – 36.9%) and with UC was 32.6% (95% CI 28.6 – 36.8%). IUD use was much less common with prevalence of 6.3% (95% CI 4.8 – 8.1%) among CD patients and 7.0% (95% CI 5.0 – 9.4%) among UC patients.

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 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 lower prevalence of exposure to hormonal contraception compared to 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 hormonal contraception use did not significantly differ between women receiving GI care in private versus academic settings (adjusted PR = 1.05, 95% CI 0.83 – 1.33). Compared to women with no risk factors for thrombosis, women with one risk factor for thrombosis were not significantly less likely to receive hormonal contraception (unadjusted PR = 0.91, 95% CI 0.76 – 1.08; adjusted PR = 0.94, 95% CI 0.76 – 1.08), nor were women with two 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 use of non-estrogen hormonal contraception was strongly associated with risk factors (table S-1). In the analysis assuming the strongest potential for bias (15% of women using non-estrogen hormonal contraception and those with any VTE risk factors being twice as likely to use the non-estrogen hormonal contraception), the estimated prevalence of estrogen-containing contraception was estimated to be 31%–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; figure 2).

## Discussion

In women with IBD who belong to a large Internet cohort, the use of hormonal contraception was widespread (CD prevalence = 33.7, UC prevalence = 32.6%). We did not find evidence that hormonal contraception use was less common among women with risk factors for thrombosis. To the contrary, point estimates of the prevalence ratio were close to the null. The absence of such a finding in spite of good statistical precision speaks to an opportunity for prevention because rates of thromboembolism are elevated among patients with IBD compared to the general population. Practice guidelines suggest that hormonal contraception containing estrogen should be avoided even in healthy patients with multiple risk factors for thrombosis or atherosclerotic disease.<sup>36–38</sup> There was 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 to the general population.<sup>4</sup> Reports of the rate of deep vein thrombosis in population-based studies suggest an incidence rate of 1–5 per 1,000 person-years.<sup>5–10</sup> Beyond the concern for venous thromboembolism in general, mesenteric vein thrombosis is increasingly recognized as clinically significant among patients with IBD, particularly those with a history of surgery.<sup>39, 40</sup> Patients with IBD experience venous thromboembolism at a younger age and with greater mortality than the general population.<sup>41, 42</sup>

Our findings are generally consistent with the prior literature in that women with IBD in this study used contraception at a higher rate than in the general population.<sup>43</sup> In a study with mean age of 28 years, the reported rate was 40.5%.<sup>17</sup> In a study with mean age of 32 years, the rate of oral contraception use was 51%.<sup>44</sup> A study set in Cape Town, South Africa, reported a rate of 38.6% at a mean age of 31 year, but comparison may be limited by cultural differences.<sup>20</sup> These studies of IBD patients reported much higher usage than in the National Survey of Family Growth (NSFG), which reported 22.2% use among women 15 to 24, 16.9% among women 25 to 34, and 9.7% among women 35 to 44 years of age.<sup>45</sup> Studies have suggested 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 demographic and other characteristics.

Women in the present study, with recruitment from June 2012 to the present day, were more likely to use IUD's than in the NSFG from 2011 to 2013. This difference may reflect the young, highly educated women in the present 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 IBD patients.

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.<sup>17, 18, 46</sup> HC may alleviate symptoms related to the menstrual cycle in some women with IBD.<sup>47</sup> Despite this, patients with two or more risk factors for thromboembolism in addition to IBD would need significant benefits from estrogen-based as compared to other methods to justify the increased risk for thrombosis. Although it is unlikely 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 chose 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 gender. 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.<sup>48, 49</sup> This study also has several limitations. As with any survey there is a potential for selection bias. This cohort likely represents a better educated, English speaking, and younger population of Internet users as compared with the general population.<sup>50, 51</sup> Our analysis of the number of additional risk factors among patients with IBD assumes the impact of each risk factor on decision-making is equal and additive. This doesn't capture the complex reality of clinical decision making or reflect the varying magnitude of risk factors. Nonetheless, this imperfect model has utility to show that clinicians and patients in general don't 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.<sup>52, 53</sup> 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).<sup>24</sup> For combined oral contraceptives, the meta-analytic risk ratio for 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.<sup>54–57</sup> We evaluated the potential for bias due to imperfect ascertainment of exposure to estrogen-based contraception. Use of progesterone-only contraceptive pills is uncommon at 0.4%, but progesterone-only implants or patches accounted for 4.2% of NSFG respondents and Depo-Provera accounted for 10.6%.<sup>58, 59</sup> 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 IBD patients 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 hormonal contraception in IBD patients.

In summary, women in an Internet cohort of subjects with IBD reported using hormonal contraception, a proxy for estrogen-based contraception, at rates greater than the general population. Use of HC among women with IBD was not limited in subjects with multiple additional risk factors for thrombosis. Though 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.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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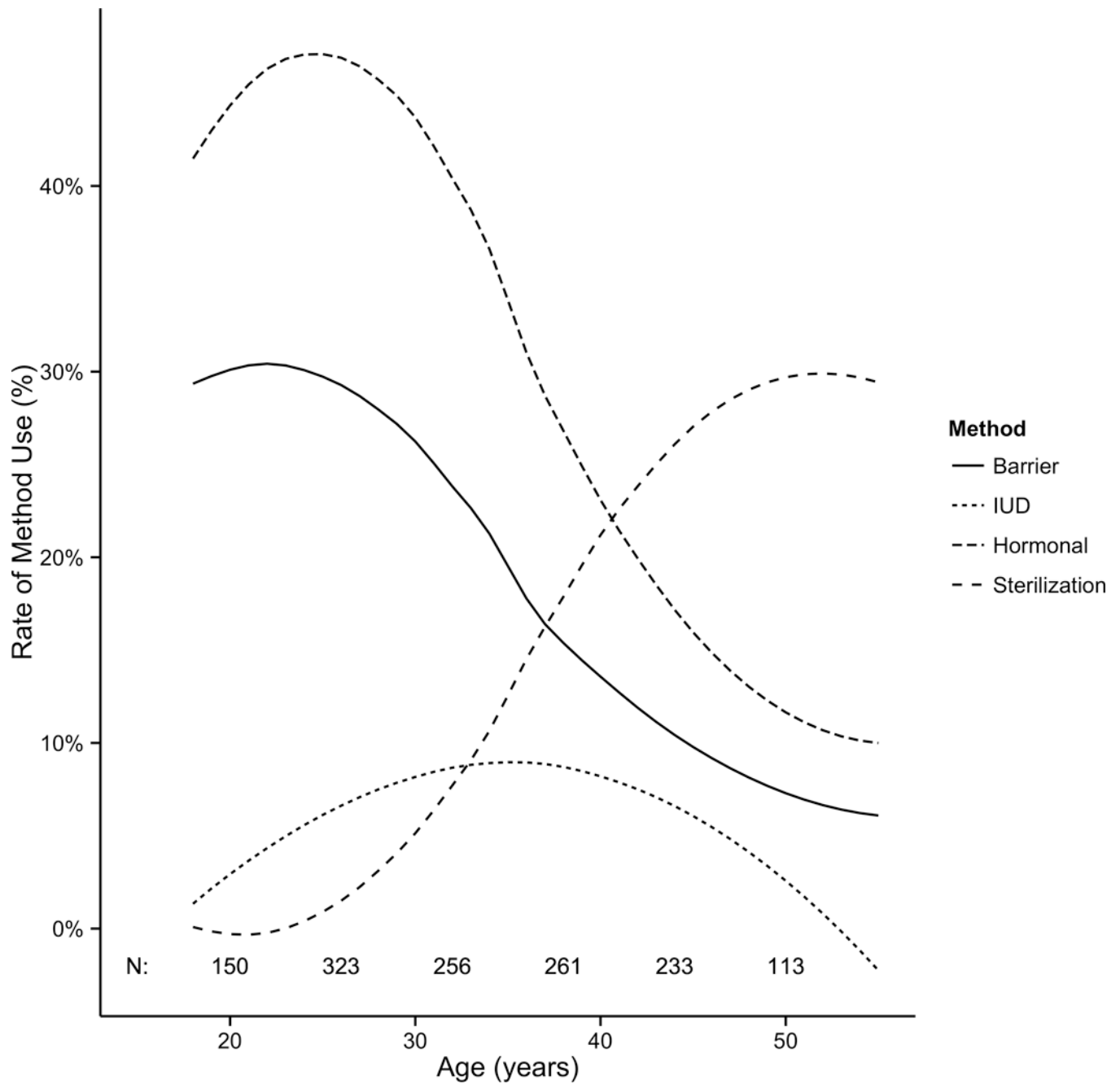
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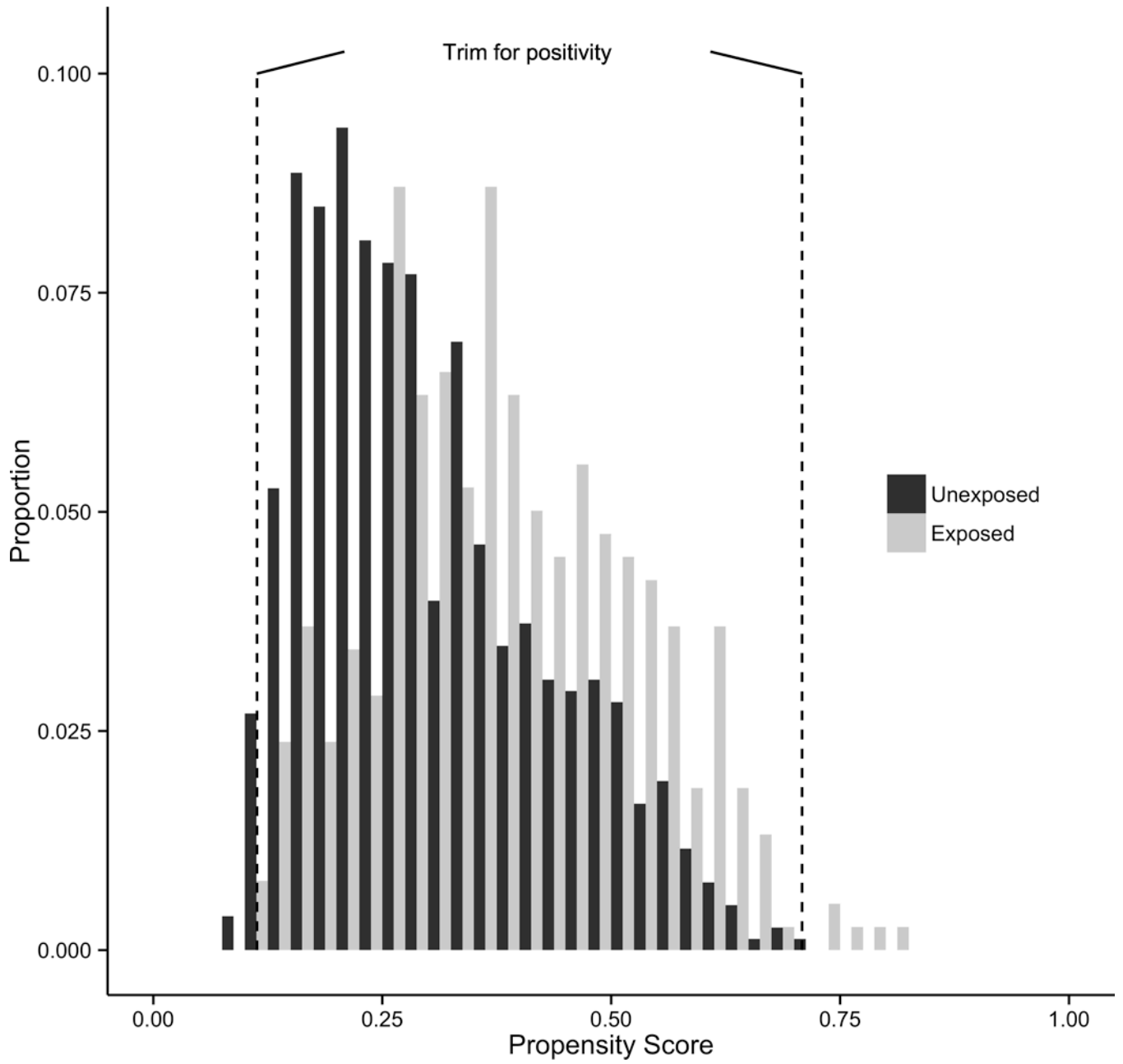


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**Figure 1.** Trends in Birth Control Methods by Age of Respondent among 1,340 Women with Ulcerative Colitis or Crohn's Disease among Patients at Risk for Using Contraception.



**Figure 2.** Distribution of Propensity Scores by the Exposure, Having One or More Risk Factors for Deep Vein Thrombosis, Compared to No Risk Factors.

Baseline Demographic Characteristics of 1,340 Patients with Ulcerative Colitis (UC) or Crohn's Disease (CD) who Responded to the Fertility Questions of the CCFA Partners Survey and Were Included for Analysis.

**Table 1**

Patient Characteristic	Ulcerative Colitis		Crohn's Disease		Total	
	N	Percent	N	Percent		
Age – Under 25	62	12.3	503	142	17.0	837
25 to 34	187	37.2	503	306	36.6	837
35 to 44	162	32.2	503	255	30.5	837
45 to 55	92	18.3	503	134	15.9	837
BMI – Underweight (<18.5 kg/m <sup>2</sup> )	27	5.5	493	52	6.3	828
Normal (18.5–24.9 kg/m <sup>2</sup> )	305	61.9	493	482	58.2	828
Overweight (25.0–29.9 kg/m <sup>2</sup> )	92	18.7	493	161	19.4	828
Obese ( ≥ 30.0 kg/m <sup>2</sup> )	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

**Table 2**  
Baseline Clinical Characteristics of 1,340 Patients with Ulcerative Colitis (UC) or Crohn's Disease (CD) who Responded to the Fertility Questions of the CCFA Partners Survey and Were Included for Analysis.

Patient Characteristic	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:						
Aminosalicylate	343	68.2	503	271	32.4	837
Corticosteroid	78	15.5	503	131	15.7	837
Immunomodulator*	112	22.3	503	300	35.8	837
Biologic <sup>†</sup>	99	19.7	503	378	45.2	837

PCP, primary care physician; GI, gastroenterologist.

\* Includes azathioprine, 6-mercaptopurine, cyclosporine, tacrolimus, and methotrexate.

<sup>†</sup> Includes TNF- $\alpha$ , integrin, and IL-12/23 targeted therapies.



Prevalence and 95% Confidence Limits (CL) of Birth Control Use among 1,340 Responding Patients with Crohn's Disease and Ulcerative Colitis.

Table 3

	Age 18 to 34		Age 35 – 44		Age 45 – 55	
	Prevalence (%)	95% CL	Prevalence (%)	95% CL	Prevalence (%)	95% CL
Any method – Crohn's disease	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)
Intrauterine device	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 – ulcerative colitis	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)
Intrauterine device	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)

Adjusted and Unadjusted Prevalence Ratios (PR) and 95% Confidence Interval (CI) for Hormonal Contraception in Women with IBD who Answered Fertility Questions and were at Risk\* as a Function of the Number of Established Risk Factors for Deep Vein Thrombosis.

**Table 4**

Patient Characteristic	N	Total	Unadjusted		Adjusted	
			PR	95% CL	PR	95% CL
Current active Disease <sup>§§</sup>	543	1,197	1.00	(0.86–1.17)	0.96	(0.82–1.12)
Current corticosteroid use <sup>§</sup>	209	1,339	0.96	(0.77–1.18)	0.93	(0.75–1.15)
Current smoking <sup>‡</sup>	83	1,339	1.02	(0.72–1.35)	1.17	(0.89–1.53)
Body mass index (kg/m <sup>2</sup> ) - Normal <sup>§</sup>	786	1,323	1.00	(ref.)	1.00	(ref.)
Body mass index (kg/m <sup>2</sup> ) - Underweight	79	1,320	0.83	(0.57–1.14)	0.62	(0.45–0.86)
Body mass index (kg/m <sup>2</sup> ) - Overweight	253	1,320	0.80	(0.64–0.98)	0.81	(0.67–0.97)
Body mass index (kg/m <sup>2</sup> ) - Obese	202	1,320	0.77	(0.60–0.97)	0.88	(0.73–1.05)
No risk factors for thrombosis <sup>§**</sup>	904	1,339	1.00	(ref.)	1.00	(ref.)
One risk factor for thrombosis	379	1,339	0.91	(0.76–1.08)	0.94	(0.80–1.11)
Two or more risk factors for thrombosis	56	1,339	0.89	(0.56–1.28)	1.10	(0.83–1.45)

IBD, inflammatory bowel diseases; CD, Crohn's disease; UC, ulcerative colitis.

\* At risk for hormonal contraception was defined as sexually active, not pregnant or breastfeeding, pre-menopausal, and not trying to conceive.

§ Active disease is defined as Simplified Crohn's Disease Activity  $\geq$  150 or Simple Clinical Colitis Activity Index  $\geq$  2.

§ Adjusted for age, current smoking, CD versus UC, prior surgery, and prior hospitalization.

‡ Adjusted for age, CD versus UC, prior surgery, and prior hospitalization.

\*\* Risk factors included corticosteroid use, smoking, and obesity.