The Influence of Hormonal Fluctuation on Inflammatory Bowel Disease Symptom Severity—A Cross-Sectional Cohort Study

Vineet S. Rolston,[*] Laleh Boroujerdi,[†] Millie D. Long,[‡] Dermot P. B. McGovern,[*] Wenli Chen,[‡] Christopher F. Martin,[‡] Robert S. Sandler,[‡] John D. Carmichael,[*] Marla Dubinsky,[§] and Gil Y. Melmed, MD, MS[*]

Background: Many women with inflammatory bowel disease (IBD) report changes in symptoms in association with hormonal changes during menses, pregnancy, and hormonal contraceptive use, suggesting a hormonal influence on disease activity. We aimed to identify and characterize IBD symptom fluctuations in women during times of hormonal variation.

Methods: From June 2012 through September 2012, women enrolled in Crohn's and Colitis Foundation of America Partners , an online Internet cohort of patients with IBD, were invited to participate in this study. Using a 5-point Likert scale, participants were asked to rate symptom changes during their menstrual cycle, pregnancy, the postpartum period, and after menopause. Clinical and demographic differences were assessed using univariate and multivariable methods.

Results: A total of 1,203 female patients with Crohn's disease (CD) and ulcerative colitis (UC) participated (64% CD, 34% UC). Over half of the women with IBD reported worsening symptoms during menses. Symptom changes were similar between women with CD vs UC, except in pregnancy, where symptom worsening during pregnancy was more commonly seen in UC than CD ($P = 0.02$). Overall, women reporting symptom worsening were younger at the time of IBD diagnosis ($P < 0.01$), had lower quality of life (SIBDQ) scores ($P < 0.01$), and had a higher BMI (25 vs 24) than women without symptom worsening.

Conclusions: Women with IBD report changes in symptom severity during times of hormone fluctuation. Further clarification of the role of hormones in IBD is warranted in order to understand these relationships and to identify potential management strategies for women with IBD and hormonally sensitive gastrointestinal symptoms.

Key Words: inflammatory bowel disease (IBD), Crohn's disease, ulcerative colitis, hormonal fluctuation

INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic intestinal inflammatory disorder, classified as either Crohn's disease (CD) or ulcerative colitis (UC). Many women with IBD report fluctuation in gastrointestinal symptoms during their menstrual cycle, with both improvement and worsening at different phases.[3] As treatment and management of IBD relies, to some extent, on patient-reported symptoms, further understanding of factors contributing to alteration of gastrointestinal symptoms is warranted.

Previous literature has sought to characterize changes in patient-reported symptoms during times of hormone fluctuation. Studies on the effects of pregnancy on IBD have focused on risks of disease relapse and pregnancy outcomes, whereas, symptom changes during pregnancy have not been fully characterized.[4–6] However, these studies have been performed in relatively small cohorts, and no single study has comprehensively assessed IBD symptoms during menses, pregnancy, and menopause within the same cohort.

The aim of this study was to survey a large cohort of women with IBD and characterize the influence of states associated with known hormonal fluctuations on symptoms. We sought to clarify whether times of hormonal fluctuation are associated with self-reported symptom changes, and to further clarify demographic and clinical characteristics of women with "hormonally sensitive" IBD symptoms.

METHODS

Study Design and Patient Selection

We performed a cross-sectional study using a large internet-based cohort of patients with IBD (Crohn's and Colitis Foundation of America [CCFA] Partners). CCFA Partners is an Internet cohort of patients with IBD who complete baseline and twiceyearly online surveys about their disease course and various patient-reported outcomes. Inclusion criteria for this cohort include individuals with UC and CD over 18 years of age, and access to the

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*F.Widjaja Foundation Inflammatory Bowel and Immunobiology Research Institute, Cedars-Sinai Medical Center, Los Angeles; †UCLA, Olive View Medical Center, Los Angeles; ‡Division of Gastroenterology and Hepatology, University of North Carolina at Chapel Hill; §Susan and Leonard Feinstein IBD Center, Icahn School of Medicine, Mount Sinai New York.

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Address correspondence to: Gil Y. Melmed, MD, MS, 8730 Alden Dr, Thalians Bldg 239E, Los Angeles, CA 90048. E-mail: Gil.Melmed@cshs.org

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Internet.[8] IBD diagnosis has been validated in a subset of the cohort, with 97% accuracy for both IBD diagnosis and subtype (CD or UC).[9]

Through CCFA Partners, women with IBD were invited to participate in an online survey between June 2012 and September 2012 through rolling invitations until the intended sample size was achieved.

Instruments

We developed a 16-item questionnaire with input from clinicians and researchers experienced in the management of women with IBD, hormonal disorders, and survey design. This survey was then evaluated by the CCFA Partners committee to ensure the survey was commensurate with other CCFA Partners surveys. The survey asked respondents to selfassess changes in their baseline disease activity in the historical context of menarche, menses, pregnancy, menopause, and hormone-replacement therapy (HRT). Symptom changes were recorded using a 5-point Likert scale (much worse, somewhat worse, no change, somewhat better, and much better). Disease activity at the time of the survey was assessed using validated instruments: the short Crohn's Diseases Activity Index (sCDAI) for subjects with CD;[10] and the Simple Clinical Colitis Activity Index (SCCAI) for subjects with UC).[11] Additionally, disease-specific, health-related quality of life was measured using the short inflammatory bowel disease questionnaire (SIBDQ). The SIBDQ is a 10-item questionnaire with graded responses for each item from 1 (poorest) to 7 (highest). Higher scores suggest a better health-related quality of life. The use of SIBDQ has been previously validated to detect changes in health status among patients with IBD.[12] Compliance was assessed by using the Morisky Medication Adherence Scale, and classified as low, medium, and high.[8]

Statistical Analysis

The primary measure was "hormone sensitivity," defined by the subjective experience of an extreme change in symptoms ("much better" or "much worse") associated with at least one of the following hormonal states: menarche, menses, ovulation, pregnancy, menopause, and hormonal contraceptive use. We aimed to identify 400 women with hormonally sensitive IBD symptoms, and we assumed a 1:2 ratio of women with hormonally sensitive symptoms versus those without hormonally sensitive symptoms. Based on this assumption, we aimed for a total sample size of 1,200 for the present study. The population was described using standard descriptive statistics including proportions, means, and standard deviation. Additionally, we assessed symptom severity at defined periods of hormone fluctuation, ie,: menses, ovulation, menopause, and menarche, acknowledging that not all subjects would have experienced all of these events. The populations were stratified for CD and UC to compare disease-type with reported symptom severity. Tests for differences were performed using univariate and multivariate regression methods, using STATA (version 12.0, College Station, TX). Confidence intervals were 95%, and $P < 0.05$ was considered to be statistically significant.

RESULTS

A total of 1,202 female patients enrolled in the study, including 64% with CD , 34% with UC, and 2% with indeterminate colitis. The median age of respondents was 43 years (interquartile range 31–55), and the mean duration of IBD was 11 years (interquartile range 5 to 21). Further characteristics of the group are listed in Tables 1 and 2.

IBD Symptoms During Menses

Just over half of women with CD and women with UC reported somewhat worse or much worse symptoms during their menstrual periods (53% of CD respondents, 51% of UC respondents) (Fig. 1). Results were similar when we analyzed a subgroup of women who reported regular and predictable menses, with 67% of women reporting somewhat worse or much worse symptoms during menses (68% of CD respondents, 66% of UC respondents).

Women who reported worsening of symptoms during menses (n = 619) were younger (26 years *vs.* 34 years ($P < 0.01$), and they had an overall decreased quality of life (median SIBDQ 4.9, (IQR 3.5–5.7)), relative to women who reported no symptom changes during menses (median SIBDQ 5.2 (SD 4.3–5.9), $P =< 0.01$). In addition, women with low medication compliance had worse symptoms during menses (42% and 23% ,respectively, $P < 0.01$). Of note, reporting of medication compliance was ascertained at the time of survey response using the Morisky Medication Adherence Scale, rather than at reporting of symptoms during menses.

IBD Symptoms Two Weeks Before Menses (Ovulation)

During ovulation (2 weeks before the onset of menses), approximately 79% reported no change in their IBD symptoms (Table 3). Rates of symptom improvement or worsening were similar between women with CD and UC.

IBD Symptoms During and After Pregnancy

Among women with IBD who had been pregnant at least once after their diagnosis with IBD (n = 270), 52% reported an improvement of symptoms (somewhat better or much better) during pregnancy (57% CD, 44% UC) (Fig. 2). Among women with a prior pregnancy, more women with CD as compared to UC reported improvement in symptoms during pregnancy (59.3% vs 47.8%, $P = 0.01$ overall chi square), and more women with UC as compared to CD reported worsening of symptoms during pregnancy (32.6% vs 16.8%, $P = 0.005$). Those women with CD who reported worsening symptoms during pregnancy also reported worse SIBDQ scores at the time of the survey (5.2 vs 4.8, $P = 0.03$).

IBD Symptoms During Menopause

Four hundred and fifty-six women reported being post-menopausal, of whom 24% were taking HRT. About two thirds of post-menopausal women (n = 295) reported no change in symptoms due

TABLE 1. Characteristics of the Population (N = 1,202)

Characteristics	N	Percent*
Age (years) (mean, IQR)	1202	43 (31–55)
Type of IBD		
Crohn's disease	771	64.1
Ulcerative colitis	405	33.7
Indeterminate colitis	27	2.2
Duration of disease (years) (median, IQR)	1198	11 (5–21)
BMI (median)	1185	24.4 (21.3–28.7)
Ostomy (% yes)	82	6.8
Education		
High school or less	93	8.2
College +	1039	91.8
Smoking (ever)	446	37.1
Disease activity		
sCDAI	688	121 (72–187.5)
SCCAI	402	3 (1–5)
Quality of life (SIBDQ) (mean, sd)	1188	5.0 (1.1)
Medication adherence		
Low	366	37.3
Medium	335	34.2
High	280	28.5
Current medications		
5-ASA (oral)$_a$	496	41.3
5-ASA (rectal)$_a$	103	8.6
Biologic anti-TNF$_b$	411	34.2
Thiopurine	272	22.9
Methotrexate	3	3.6
Corticosteroids (oral)	112	9.4
Corticosteroids (rectal)	71	5.9
Entocort	49	4.0
Gynecologist/Hormonal History		
Age at menstruation (mean, sd)	1184	12.9 (3.3)
Age at menopause (among those in menopause) (mean)	458	46.4 (8.1)
Currently taking supplements (black cohosh, soy, etc) for menopausal symptoms (among those in menopause)	40	8.7
Currently taking HRT for menopausal symptoms (among those in menopause)	93	20.2
Hormonal contraceptives (ever use, % yes)		
Birth control pills	613	51.0
Hormone injection	44	3.7
Hormone patch	35	2.9
Hormone ring	64	5.3
Hormone IUD$_c$	45	3.7
Other hormonal contraception	10	0.8
Never taken hormonal contraception	96	8.0
Pregnancy (% ever)	674	56.3
Pregnancy after IBD diagnosis	315	26.2
Times pregnant after IBD diagnosis	315	2 (1–2), range 1–6
Age at first pregnancy after IBD diagnosis	272	29 (26–32)
Breastfeeding among those with pregnancy (% yes)	197	73.0

*unless otherwise stated. $_a$ASA: acetylsalicylic acid, $_b$Anti-TNF: anti-tumor necrosis factor, $_c$IUD: intrauterine device.

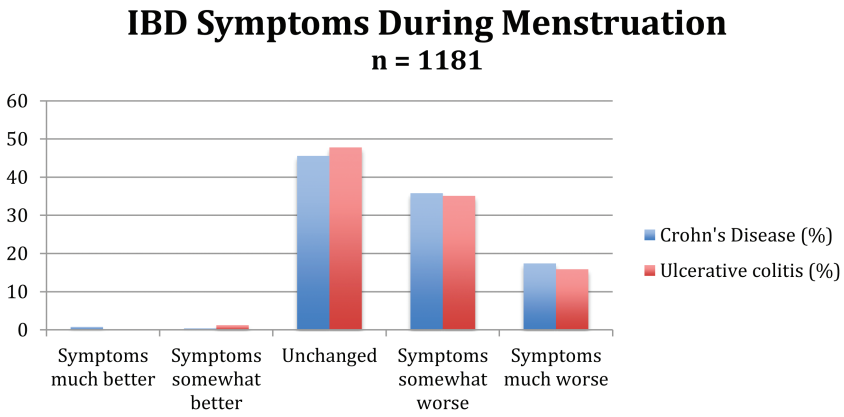

FIGURE 1. IBD Symptoms During Menstruation.

TABLE 2. Description of Menstruation

	N	Percent
Not started	3	0.2
Regular/predictable menses	469	39.0
Irregular menses	178	14.8
No menstrual period for > 1 year (not menopausal)	67	5.6
Post menopausal	338	28.1
Hysterectomy	129	10.7
Currently pregnant	19	1.6

TABLE 3. What Happens to IBD Symptoms 2 Weeks Before Menstrual Period

	N	percent
Symptoms much better	10	0.9
Symptoms somewhat better	22	1.9
Unchanged	928	78.6
Symptoms somewhat worse	169	14.3
Symptoms much worse	51	4.3

to menopause itself, while 16% reported improvement in symptoms during and after menopause (Table 4).

Women with worsened symptoms after menopause were older at the time of receiving an IBD diagnosis compared to those who did not report worsened symptoms (44 years old at time of diagnosis vs 32 years old, $P < 0.01$). Among postmenopausal women reporting worse symptoms, disease worsening was independent of smoking and BMI.

IBD Symptoms While on Exogenous Hormones

Women were asked to identify whether they had taken hormone supplementation during their disease course, including HRT and hormonal contraceptives. Six hundred and thirteen women reported ever using hormonal contraceptives, and 93 reported using HRT for menopausal symptoms. Reasons for the use of hormonal contraceptive included pregnancy prevention (60%), regulation of menses (21%), dysmenorrhea (13%), and to improve IBD symptoms (2.3%).

Among those using HRT at time of survey response, 61% reported no change in IBD symptoms with HRT, while 31% stated they "didn't know" whether HRT influenced symptoms. Among those who were current or prior users of hormonal contraceptives, 83% reported no change in IBD symptoms, whereas 3% reported improvement, and approximately 7% reported worsening of symptoms from hormonal contraceptive use, identified as symptoms "somewhat worse" and symptoms "much worse". (Tables 5 and 6).

Hormone Sensitivity

In a separate analysis, we classified 413 women (34%) with hormonally sensitive symptoms, reporting that symptoms were much better or much worse at a time of hormonal fluctuation. These individuals with hormonally sensitive symptoms had lower overall SIBDQ scores (Table 7). Additionally, we found that women with hormonally sensitive symptoms tended to be younger at the time of IBD diagnosis (28 years vs 31 years $P < 0.01$) and had IBD for a longer duration of time (13 years vs 9 years $P < 0.01$) compared to those who were not hormonally sensitive.

Additionally, women with UC who had hormonally sensitive symptoms were more likely to have higher clinical disease activity scores, but this was not seen among women with CD (Table 8).

DISCUSSION

We aimed to clarify associations of symptom changes in women with IBD during several different times of hormonal fluctuations. We found that many women have hormonally sensitive symptoms at various times of hormonal changes, defined as having significant changes in their symptoms at various phases of hormonal fluctuation. Over half of women had worsening of symptoms during menses. In general, symptom changes were not different among women with CD versus. UC, with the exception of more significant reported disease worsening during pregnancy in women with UC relative to CD among all women reporting worsening of

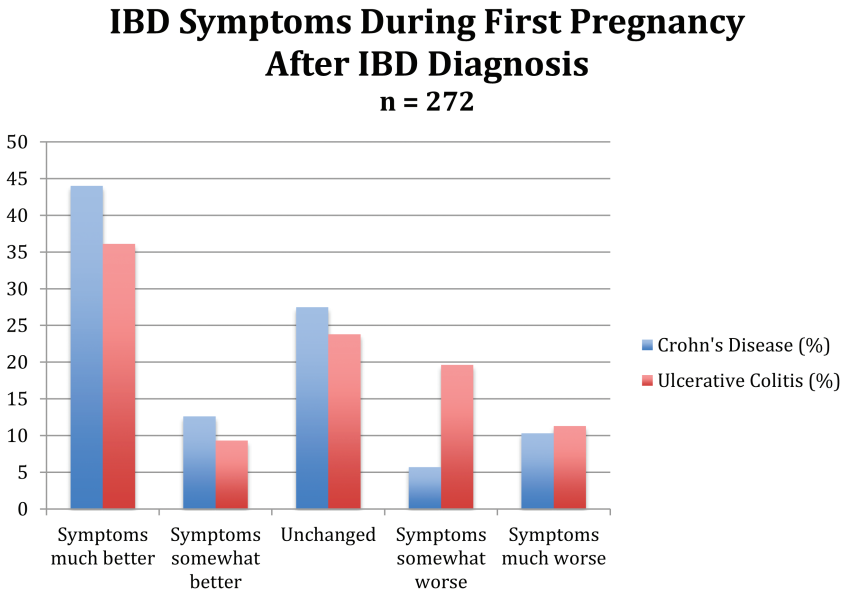

FIGURE 2. IBD Symptoms During First Pregnancy After IBD Diagnosis.

TABLE 4. What Happens to IBD Symptoms After Menopause Among Those in Menopausewith CD/UC

	Crohn's disease		Ulcerative colitis	
	n	percent	n	percent
Symptoms much better	20	6.7	10	6.4
Symptoms somewhat better	29	9.7	14	8.9
Unchanged	195	65.2	100	63.7
Symptoms somewhat worse	30	10.0	12	7.6
Symptoms much worse	25	8.4	21	13.4

TABLE 5. What Happens to IBD Symptoms After Taking HRT/Supplements Among Those in Menopause (n = 111)

	Crohn's disease		Ulcerative colitis	
	n	percent	n	percent
Symptoms much better	6	7.9	2	5.7
Symptoms somewhat better	3	4.0	1	2.9
Unchanged	67	88.2	32	91.4
Symptoms somewhat worse	0	0	0	0
Symptoms much worse	0	0	0	0

TABLE 6. What Happens to IBD Symptoms After Starting Birth Control Pills (n = 612)

	Crohn's disease		Ulcerative colitis	
	n	percent	n	percent
Symptoms much better	12	3.1	6	2.6
Symptoms somewhat better	26	7.0	15	6.6
Unchanged	319	83.3	187	81.7
Symptoms somewhat worse	14	3.7	14	6.1
Symptoms much worse	11	2.9	7	3.1

symptoms during pregnancy (Fig. 2). In contrast, pregnancy was associated with overall improved symptoms in the majority of women with IBD, regardless of disease subtype.

Approximately one-third of our cohort met criteria for having hormonally sensitive symptoms, ie, reported extreme symptom changes (much better or much worse) at a time of hormonal fluctuation. This finding suggests the need to ask about symptom changes at the time associated with hormonal fluctuations in all women with IBD, and additional effort to consider this association when differentiating hormonally-related symptom fluctuation from disease exacerbation in the clinical setting. Although we asked women to identify symptoms related to their IBD, it is unclear whether self-reported changes in gastrointestinal symptoms truly reflect worsening inflammatory symptoms, or perhaps hormonally-triggered motility disturbances leading to gastrointestinal manifestations.

Many of our findings are consistent with previously published literature, although some key differences are noted. Several studies have found that women with CD were more likely to report worsening of symptoms at the time of menses than women with UC. Several studies found higher reported diarrheal symptoms during the menstrual cycle among women with CD compared to those with UC.[3,13,14] In contrast, we found that both CD and UC were associated with symptom worsening during menses, which may be a function of assessing a larger sample size compared to other studies. Consistent with prior literature, our cohort did

TABLE 7. Disease Activity Between Hormone Sensitive and Hormone Insensitive

Individuals (n = 1075)			
Severity Score	Hormone Sensitive Average (SD)	Hormone Insensitive Average (SD)	*P*-value
SIBDQ	4.7 (1.2)	5.0 (1.1)	<0.01

TABLE 8. Disease Activity Between Hormone Sensitive and Hormone Insensitive

Individuals (n = 1075)			
Severity Score	Hormone Sensitive Average (IQR)	Hormone Insensitive Average (IQR)	*P*-value
CD (SCDAI)	128 (79–205)	107 (72–184)	0.64
UC (SCCAI)	4 (2–6)	3 (1–5)	<0.01

not report a significant change in symptoms after menopause.[15] Previous studies have demonstrated that estrogen surges during the menstrual cycle appear to cause decreases in gut motility, increased gut permeability, and heightened pain perception.[16] During menopause, the fluctuations in hormones, estrogen in particular, are more gradual than they are in premenopausal women.[17] We hypothesize that times of hormonal surge, rather than depletion as seen in the postmenopausal period, is a contributing factor to worsening GI symptoms.

The use of exogenous hormones including HRT and hormonal contraceptives were not associated with changes in reported symptom severity in our cohort, similar to findings previously published.[18]

Women with UC who met the criteria for having hormonally sensitive symptoms were more likely to have higher disease activity scores, unlike women with CD who had hormonally sensitive symptoms. This finding differs from prior work by Saha et al, who demonstrated that women with CD who reported dysmenorrhea symptoms, including diarrhea and abdominal pain, were more likely to have higher disease activity scores.[19] These findings need to be interpreted cautiously in light of the self-reported nature of our study, which may more directly correlate with endoscopic disease activity scores in patients with UC relative to CD.[20,21]

Previous studies have reported disparate findings with regard to the effect of pregnancy on symptoms in IBD. We found that more than half of the women reported improvement of symptoms during pregnancy. Notably, while the majority of women reported improved symptoms, there was a higher proportion of women with UC compared to women with CD who reported worsening of symptoms. This discrepancy of symptoms during pregnancy between women with UC and CD has been previously noted in a survey of 209 women, where those with UC had increased chances of relapse of disease, unlike those with CD.[4] Other studies have focused on rates of disease recurrence and/or relapse during pregnancy, and several studies, including a metaanalysis by Abhyankar et al that demonstrated an increased risk for IBD relapse during pregnancy, influenced by disease activity at time of conception.[6] These studies must be interpreted with caution, however, as several represent findings before the introduction of biologic therapy for treatment of IBD.

A number of mechanisms explaining the relationship between worsening GI symptoms and menstruation have been suggested. One theory suggests that elevated prostaglandin production during menses may be responsible for increased contraction of colonic smooth muscle.[22] Additional studies have demonstrated the influence of estrogen surge on gut permeability, gut motility, and pain perception as described above.[16] Other studies have demonstrated protective effects of pregnancy on rheumatoid arthritis, multiple sclerosis, and psoriasis, with proposed mechanisms including immunomodulation of T cell activity during pregnancy, thereby reducing inflammation-driven symptoms in these women.[23] The molecular basis of IBD involves a complex interplay between inflammatory modulators and key cytokines including prostaglandins and variations in T cell subsets. A pivotal cytokine in IBD is TNFα, which has been shown to be down-regulated in pregnancy, itself a physiological state of immune tolerance in some respects.[24] It may be that for some women with IBD, alterations in these profiles may lead to improved (or worsened) disease activity as a result of normal pregnancy driven changes in immunity.

Our study has several limitations. Patient responses to surveys may be influenced by recall bias. Our survey asked participants to report symptoms at various times of hormonal fluctuation, including possible remote episodes such as pregnancy or during the premenopausal period. Prior work has demonstrated that recall of symptoms in the premenstrual period is particularly subject to recall bias and influenced by social stressors, anxiety, and depression.[14,25–27] Additionally, our survey also included data such as BMI and SIDBDQ at the time of survey participation, which may not reflect these values at the time of reporting historical symptoms. Additionally, we recruited self-motivated and highly-educated participants who were already participating in the CCFA Partners cohort, which may limit the generalizability of our results. Our surveys relied on subjective reporting of symptoms without objective assessments to correlate with true biologic disease activity. As demonstrated in studies by Kane et al, women with irritable bowel syndrome also report GI symptoms during menses, and it is difficult to objectively attribute changes in GI symptoms to IBD disease activity based solely on the patient's experience.[3] Although e we assessed medication adherence using the Morisky Medication Adherence Scale at the time of survey response, we did not ask participants about medication adherence during specific times of hormonal fluctuation such as pregnancy or during menses, which may be historical in nature and may influence symptom reporting by our participants. When women were asked within our survey about use of exogenous hormones, we did not differentiate between vaginal HRT versus oral therapy, which may also influence these results.

Another limitation within our survey tool was the lack of piloting before implementation of this survey to members of the CCFA, however, it was iteratively developed with input by experienced clinicians and survey design specialists. Finally, we did not ask participants if they had undergone hysterectomy or oophorectomy, and hence the inclusion of such participants also may bias our results.

Despite these limitations, our study demonstrates that women with IBD report symptom changes during times of hormone fluctuation, particularly during menses and pregnancy. In particular, women with UC experience a greater likelihood of worsening symptoms than women with CD. Additionally, women with lower SIBDQ scores and more severe disease appear to be more susceptible to these fluctuations. Women with IBD should be asked about their symptom changes during times of hormonal fluctuation, to better elucidate cycles of disease activity. Further investigations to clarify the true associations and pathogenesis of hormonally influenced changes in IBD symptoms and disease activity are warranted.

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