Published in final edited form as:

Inflamm Bowel Dis. 2013 June ; 19(7): . doi:10.1097/MIB.0b013e318281f3a9.

Dysmenorrhea in Women with Crohn's Disease: A Case-Control Study

Sumona Saha, M.D., M.S.,

Department of Medicine, Division of Gastroenterology and Hepatology, University of Wisconsin School of Medicine and Public Health

Emilie Midtling, B.S.,

Department of Medicine, Division of Gastroenterology and Hepatology, University of Wisconsin School of Medicine and Public Health

Erica Roberson, M.D., M.S.,

Department of Medicine, Division of Gastroenterology and Hepatology, Oregon Health and Sciences University

Veena A. Nair, Ph.D.,

Department of Radiology, University of Wisconsin School of Medicine and Public Health

Arnold Wald, M.D., and

Department of Medicine, Division of Gastroenterology and Hepatology, University of Wisconsin School of Medicine and Public Health

Mark Reichelderfer, M.D.

Department of Medicine, Division of Gastroenterology and Hepatology, University of Wisconsin School of Medicine and Public Health

Introduction

Abdominal and pelvic symptoms in young women with Crohn's disease (CD) are often attributed to inflammatory bowel disease (IBD) when, in fact, other entities may be responsible. Dysmenorrhea, or painful menstruation, is the most common disorder of reproductive-aged women and has symptoms which overlap with active CD [1, 2].

Correspondence Please address correspondence regarding this manuscript to: Sumona Saha, M.D., Division of Gastroenterology and Hepatology, University of Wisconsin School of Medicine and Public Health, UW Medical Foundation Centennial Building, 1685 Highland Avenue, Rm 4224, Madison, WI 53705, Phone: 608-263-1995, Fax: 608-265-5677, ssaha@medicine.wisc.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Disclosures

The authors have no conflicts of interest to disclose with regards to this manuscript

Writing Assistance

Not applicable

Author Contributions

Sumona Saha: concept and design; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content; statistical analysis; obtained funding

Emilie Midtling: acquisition of data

Erica Roberson: concept and design; critical revision of the manuscript for important intellectual content

Veena Nair: statistical analysis

Arnold Wald: concept and design; critical revision of the manuscript for important intellectual content

Mark Reichelderfer: concept and design; critical revision of the manuscript for important intellectual content; study supervision

Determining the prevalence of dysmenorrhea and its contribution to overall pain severity and to perceived CD activity may be helpful in tailoring therapy in women with CD and avoiding the over assignment of gastrointestinal (GI) symptoms to IBD.

It is well established that painful disorders of the GI tract such as irritable bowel syndrome (IBS) are frequently co-morbid with primary dysmenorrhea, with some women reporting an increase in symptoms during menstruation [3, 4]. The relationship between menstrual distress and inflammatory disorders of the GI tract such as CD is less well understood; however, prior studies suggest that menstrual symptoms may be perceived as increased CD activity due to their overlapping symptoms [5]. In addition, common pathophysiologic mechanisms may exist between the two disorders. Kane and colleagues suggested that the greater rates of diarrhea that women with IBD report during the premenstrual and menstrual phases of the cycle may be related to increased colonic contraction from intestinal prostaglandin production during these phases and/or increasing progesterone levels across the menstrual cycle [5]. It is important to note, however, that a direct correlation between plasma levels of ovarian hormones and perimenstrual symptoms has not been established [6].

To date, no study has determined the prevalence of dysmenorrhea or the impact of menstrual pain in women with CD using validated methods. Furthermore, no study has examined the relationship between dysmenorrhea and CD activity scores or between dysmenorrhea and HRQOL in women with CD. Closing this knowledge gap is imperative. The purpose of this study was to examine: 1) the impact of dysmenorrhea on overall pain severity and pain medication use in women with CD vs. healthy controls, 2) the relationship between dysmenorrhea and CD activity scores, and 3) the effect of dysmenorrhea on HRQOL in women with CD.

Methods

Subjects

We recruited women aged 18 to 48 with regular menstrual cycles, defined as cycles ranging from 24 to 35 days and lasting 4 to 6 days for 3 consecutive months prior to study entry, and with CD as determined by endoscopy or radiographic imaging. Women aged 18 to 48 with regular menstrual cycles and without CD or other major co-morbidity were recruited as controls.

Subjects (cases and controls) were excluded if they were pregnant or breastfeeding, using or recently (within 3 months) had used intradermal, injectable or intrauterine contraception, less than 3 months post-partum, within 3 years of menarche, or had been diagnosed with ulcerative colitis, indeterminate colitis, IBS or other functional bowel disorder (FBD), premenstrual syndrome, endometriosis, pelvic inflammatory disease, or other significant GI or gynecologic co-morbidity as determined by the principal investigator.

Subjects were actively recruited in the primary care and gastroenterology clinics at the University of Wisconsin Hospital and Clinics from May 2010 to July 2011.. Passive recruitment was also conducted using fliers posted on bulletin boards at the University hospital. Eligible subjects were offered \$30 for participation.

Procedures

Written informed consent was obtained. All data collection except for the Crohn's Disease Activity Index (CDAI) score was conducted at a single visit. Data elements were collected by structured interview, self-completion of validated questionnaires, or standardized data

abstraction from the medical record (see Table 1). Regarding the CDAI, cases were given a 7-day symptom diary to return by mail.

This study was approved by the Institutional Review Board at the University of Wisconsin in April 2010.

Definition of Dysmenorrhea

Dysmenorrhea was defined according to Andersch and Milsom [7] as severely painful menstruation during the past 3 months leading to missing work/school or significant life events.

Measures

Global pain severity was evaluated using a 0 to 10 scale (0=no pain to 10=worst imaginable pain). Subjects were asked to rate their pain over the past 3 months.

Menstrual symptoms were evaluated using Form C of the Moos Menstrual Distress Questionnaire (MDQ), a self-report inventory for measuring cyclical perimenstrual symptoms [8]. Form C consists of 46 items, each describing a specific symptom. Subjects are asked to rate their experience with each symptom on a 5-point scale (0=no experience of symptom; 4=symptom present and severe). Ratings of each symptom were made separately for the 3 phases of each subject's most recent cycle: menstrual (during menstruation), premenstrual (4 days before menstruation), and intermenstrual (the remainder of the cycle). The MDQ items are divided among 8 symptom scales as follows: pain, water retention, autonomic reactions, negative affect, impaired concentration, behavior change, arousal, and control. MDQ composite scores and pain subscores were calculated for each subject.

CD activity was measured using the CDAI [9] and Harvey-Bradshaw Index (HBI) [10].

Quality of life was measured using the Short Form-36 (SF-36) [11, 12], and the Inflammatory Bowel Disease Questionnaire (IBDQ) [13]. A total score and 2 standardized summary scores, the physical component summary (PCS) score and the mental health component summary (MCS) score, were calculated for each subject using the SF-36. Using the IBDQ, a total score ranging from 32 (very poor HRQOL) to 224 (perfect HRQOL) was calculated for each case along with 4 sub domain scores.

Statistical Analysis

A sample size of 118 (59 controls, 59 cases) was calculated based on a two-sided test with $\alpha = 0.05$ and $\beta = 0.80$. This is based on the published prevalence of dysmenorrhea in otherwise healthy women of 25% and a prevalence of dysmenorrhea in women with IBS of 50% which was extrapolated to be similar in women with IBD.

Descriptive statistics, including means and standard deviations for continuous variables and frequencies for categorical variables, were calculated for cases and controls using standard methods.

An overall odds ratio was calculated for having dysmenorrhea among cases and controls. Adjustment was then made for confounding factors, including young age (i.e. age < 20 years), nulliparity, depression/anxiety, heavy menses, and hormone-based contraceptive use.

To compare epidemiological and clinical characteristics, parametric and non-parametric continuous variables were compared with Student's t-test and the Mann-Whitney test respectively, and categorical variables were compared with the Chi-square test or Fisher's exact test, as appropriate. Pearson's r correlation coefficient was used for correlation

between menstrual distress scores and CD activity scores. Linear regression was performed to determine the relationship between dysmenorrhea and the disease activity scores.

All analyses were done using SPSS-PASW Statistics GradPack 17.0.

Results

Subjects

Fifty-four cases and 66 controls were recruited. The majority of cases had colonic disease only (64.8%). Thirty nine percent of cases had ileocolonic disease, 5.6% had small bowel disease only, and 3.7% had disease in other locations. Fistulas were present in 26% of cases: 16.7% had peri-anal fistulas and 9.3% had non-perianal fistulas. Five out of 54 cases (9.3%) had undergone IBD-related surgery: 1.9% had undergone partial colon resection, 5.5% were status post ileocolonic resection, and 1.9% had undergone perianal fistula drainage.

Cases and controls did not differ significantly in demographic characteristics, level of educational achievement, and social habits (Table 2). The prevalence of gynecologic surgeries did not differ significantly between cases and controls. nor did menstrual and pregnancy histories (Table 3). We found significantly higher use of non-steroidal anti-inflammatory drugs (NSAIDS) by controls compared to cases ($p<0.001$). No significant difference in aspirin or hormone use was found between the 2 groups.

Dysmenorrhea prevalence

The prevalence of dysmenorrhea was 40% in cases and 46% in controls. The odds ratio for dysmenorrhea in women with CD was 0.77 (95% CI: 0.37 to 1.60). We tested a multinomial logistic regression model for dysmenorrhea in cases with age, pregnancy, depression, heavy menses, and hormone use as covariates. The overall model was not significant nor were the likelihood ratio tests for the individual variables.

Pain Severity and Pain Medication Use

Pain scores were significantly higher in subjects with dysmenorrhea compared to those without among both cases and controls ($p<0.001$, both). When evaluating only subjects with dysmenorrhea, there was no difference in pain scores between cases and controls (Table 4).

Pain medication use of any type for menstrual pain was not significantly different in the presence or absence of dysmenorrhea among controls. NSAID use, however, was significantly higher in controls with dysmenorrhea ($p=0.005$) in contrast to lower use among cases. Greater pain medication use for menstrual pain was found for cases with dysmenorrhea vs. cases without ($p=0.0001$); however, there was no difference in NSAID use between these groups.

In women without dysmenorrhea, we found that more controls used pain relievers for menstrual pain ($p=0.002$). There was no significant difference in pain medication use of any type for menstrual pain between cases and controls with dysmenorrhea; however, controls with dysmenorrhea used more NSAIDS than did cases ($p=0.001$).

Linear regression analysis was performed with dysmenorrhea and CD as predictors for pain severity. Dysmenorrhea was highly significant ($p<0.0001$) and CD trended towards significance ($p=0.05$). Multinomial logistic regression with an interaction term between dysmenorrhea and CD did not change the model.

Menstrual Distress Questionnaire score

As expected, when comparing subjects (i.e. cases plus controls) with dysmenorrhea to subjects without dysmenorrhea, we found the MDQ composite score and the MDQ pain subscore to differ significantly between groups ($p=0.03$, both). However, when comparing cases with dysmenorrhea to controls with dysmenorrhea we found no significant differences in either score (Table 5). Differences in MDQ composite scores and MDQ pain subscores were not significantly affected by CD location; however, the study was underpowered to find such differences. The presence of perianal fistulas also did not significantly affect MDQ scores.

We performed a one-way ANOVA to examine differences between cases and controls on the MDQ pain subscore and composite score with hormone, NSAIDS, and aspirin use as covariates. Cases reported significantly higher pain than controls on the pain subscore ($p=0.04$) but no significant difference was found between groups on the composite score.

Crohn's Disease Activity Scores

The mean CDAI score (SD) for all cases was 108.4 (80.6) and the mean HBI (SD) score was 3.4 (3.1). By either scoring system our cases, on average, were in remission. The differences in mean CDAI scores and HBI scores for cases with and without dysmenorrhea were not significant.

Pearson correlation coefficients were calculated to evaluate for correlations between CD activity and the MDQ composite score and MDQ pain subscore. The Pearson r correlation between CDAI and MDQ composite score was weakly positive ($r=0.42$, $p=0.004$) as was the correlation between CDAI and MDQ pain subscore ($r=0.44$, $p=0.003$). The correlation between the HBI score and MDQ composite score trended towards significance ($r=0.27$, $p=0.051$) and was weakly positive between the HBI score and MDQ pain subscore ($r=0.32$, $p=0.019$).

Health-Related Quality of Life

Total SF-36 scores were significantly lower in cases with dysmenorrhea compared to cases without ($p=0.016$). When comparing summary scores PCS scores, but not MCS scores, were also significantly lower ($p=0.004$) in cases with dysmenorrhea (Table 6).

The mean total IBDQ score for all cases was 168.9 (32.7). The mean total IBDQ scores for cases with and without dysmenorrhea were, 163.3 (33.3) and 173.1 (32.7), respectively. The difference in total scores was not significant; however, the difference in the systemic symptoms subscore was ($p=0.035$). No significant difference was found for the other IBDQ subscores. Univariate analysis with NSAID use and hormone use as covariates did not show any significant difference in SF-36 or IBDQ scores between cases with and without dysmenorrhea.

Discussion

Dysmenorrhea is the most common gynecologic complaint and the leading cause of school and work absenteeism among women. The prevalence of dysmenorrhea ranges widely in the literature depending on the population studied and the measurement method used [7,14–17]. Conservatively dysmenorrhea affects 25% of menstruating adults. In addition, up to 90% of adolescents may be affected [1]. While lower abdominal cramps are the most common symptom of dysmenorrhea, women may also experience nausea and vomiting, loss of appetite, diarrhea, general aching as well as irritability, sleep disturbances, and depression [18]. The severity of dysmenorrhea varies depending on its interference with daily activities

[19] and patients' perception of pain [20]. Various pain scales and scores have been used to grade the severity of dysmenorrhea [21–23].

Dysmenorrhea is categorized as primary if there is no underlying pelvic pathology or secondary if pelvic pathology is present. Prostaglandin F_2 , a potent myometrial stimulant and vasoconstrictor in the uterus, is believed to mediate primary dysmenorrhea [24]. Leukotrienes [25, 26] and vasopressin [27, 28] may also contribute. Although the distinction between primary and secondary dysmenorrhea may be used to determine treatment approach, differences in pain experience or sensitivity have not been well-established between the two groups [29].

Given the prevalence of dysmenorrhea among reproductive-aged women and its shared symptoms with CD, symptom confusion between the two entities may occur. Thus, women with CD and dysmenorrhea may perceive their disease as being more active and undergo more testing and/or medication changes than their non-dysmenorrheic counterparts. Documenting the prevalence of dysmenorrhea in women with CD and determining the relationship between dysmenorrhea, CD and pain severity are therefore important.

In this study we found dysmenorrhea was highly prevalent in women with CD, occurring in 40% of cases. We also found that it had an additive effect on global pain severity. Although the odds of dysmenorrhea was not significantly higher among cases compared to controls, prior studies suggest that menstruation causes GI symptoms, particularly diarrhea, more frequently in women with IBD compared with healthy controls and produces cyclic variation in symptoms in women with both UC and CD [30, 31]. Therefore given the prevalence of dysmenorrhea and its impact on IBD symptoms it is a co-morbidity for which screening is needed. Failure to recognize dysmenorrhea may contribute to the higher frequency of bowel symptoms reported by women with IBD compared to men [32] and lead to the erroneous conclusion that abdominal pain is solely attributed to IBD

We found no significant difference in pain medication use of any type for menstrual pain between controls with and without dysmenorrhea. However, among cases, pain medication use was significantly associated with dysmenorrhea. One possible explanation for this is that non-IBD women may be using pain medication for non-dysmenorrheic menstrual pain, whereas women with CD, who are habituated to a baseline level of pain, may only be using medications when menstrual pain is severe. With regards to NSAID use, we found the opposite trends. Controls with dysmenorrhea used significantly more NSAIDs than controls without dysmenorrhea, in contrast to cases who did not. This likely reflects the reluctance to use NSAIDs by patients with IBD given their association with increased disease activity [33] and hospitalization [34]. It also suggests that women with CD may be avoiding the preferred initial treatment of dysmenorrhea and using less effective medications for the treatment of menstrual pain [35]. Practitioners should consider on a case-by-case basis whether NSAIDs are an appropriate treatment for their dysmenorrheic IBD patients.

A secondary aim of this study was to explore the impact of dysmenorrhea on measures of CD activity and on HRQOL. Given the overlap in symptoms between dysmenorrhea and active CD we hypothesized that cases with dysmenorrhea would have higher CD activity scores compared to cases without. However, we found that neither with the CDAI nor with the HBI was there a difference between groups. Thus at least for patients with CD in remission dysmenorrhea was not associated with higher CDAI or HBI scores. We did, however, find positive correlations between the MDQ composite score and pain subscore and the CDAI and HBI. This suggests that there may be a tendency for women with CD with higher levels of menstrual distress to have higher CD activity scores. Greater perceived CD activity may lead to more health-care seeking behavior by women with co-morbid

dysmenorrhea. This, in turn, may lead to more rigorous evaluation for active disease and unwarranted changes to CD treatment regimens.

To evaluate the impact of dysmenorrhea on HRQOL among women with CD, we used both generic and disease-specific measures. We found total SF-36 scores to be lower in cases with dysmenorrhea vs. controls with dysmenorrhea. PCS scores were also significantly lower and there was a trend towards lower MCS scores. These differences may be explained by the lower HRQOL that individuals with CD experience at baseline. Although there was no significant difference in total IBDQ scores, we found that cases with dysmenorrhea scored more poorly on the systemic symptoms subscore of the IBDQ compared to cases without dysmenorrhea. This subscore is based on questions pertaining to feeling tired and worn out, energy, general wellness, sleep disturbances, and weight problems. Interestingly, the bowel symptoms subscore of the IBDQ was not affected by dysmenorrhea despite its shared GI manifestations with active CD. Nevertheless, recognizing the impact of dysmenorrhea on the physical and systemic symptoms experienced by women with CD provides another target for improving QOL in this population.

This study is potentially limited by several possible sources of bias. First, although we used a standard definition of dysmenorrhea, the perception of whether menstruation is painful is subjective, allowing for possible misclassification bias. Results from the MDQ, however, suggest that subjects did correctly self-identify as those with dysmenorrhea had greater menstrual distress scores compared to those without. Second, recall bias may have altered the assessment of menstrual pain severity and pain medication use. We used Form C of the MDQ to address this as it has been validated to retrospectively measure menstrual distress. Lastly, selection bias may have led to an overestimation of dysmenorrhea rates among non-IBD women as most of our controls were recruited from primary care clinics focused on women's health. Thus the prevalence of dysmenorrhea among our controls could be greater than the true prevalence in the general population. If this were the case, the odds of dysmenorrhea may in fact be higher in women with CD which makes its recognition even more important.

Given the paucity of data in IBD and menstruation, future directions for this work include evaluation of the effect of painful menstruation on perceived disease activity in ulcerative colitis. More precise correlation between menstrual symptoms and IBD activity is also needed. Studies with repeated use of Form T of the MDQ, a self-report instrument which prospectively records reactions or symptoms experienced by women on a specific day, a 30-day GI symptoms diary, and inflammatory markers may achieve this. In addition, intervention studies aimed at treating dysmenorrhea are needed to assess the improvement in HRQOL women with CD experience after their menstrual distress has been addressed.

Conclusions

Dysmenorrhea and CD are additive predictors for global pain severity. Dysmenorrhea in women with CD was associated with higher pain medication use for menstrual pain but not with higher NSAID use, suggesting that women with CD may be using less effective therapies to treat dysmenorrhea. Menstrual distress as measured by the MDQ positively correlates with CD activity scores suggesting that menstrual symptoms may impact perception of patients' IBD activity. This may lead to more health-care seeking behavior and/or lower health status. Lower scores in some aspects of HRQOL were also found in subjects with CD and dysmenorrhea, suggesting that dysmenorrhea is a potential target for interventions to improve the overall health status of this population. Gastroenterologists should consider this entity when evaluating pain in women with CD.

Acknowledgments

Grant Support

This project was supported by Award Number K12 HD055894 from the Eunice Kennedy Shriver National Institute of Child Health & Human Development. The content is solely the responsibility of the authors and does not necessarily represent the official views of the Eunice Kennedy Shriver National Institute of Child Health & Human Development or the National Institutes of Health.

Abbreviations

GI	gastrointestinal
IBS	irritable bowel syndrome
IBD	inflammatory bowel disease
HRQOL	health-related quality of life
FBD	functional bowel disorder
CDAI	Crohn's Disease Activity Index
MDQ	Menstrual Distress Questionnaire
HBI	Harvey-Bradshaw Index
SF-36	Short-form-36
IBDQ	Inflammatory Bowel Disease Questionnaire

References

1. Durain D. Primary dysmenorrhea: assessment and management update. *J Midwifery Womens Health*. 2004 Nov-Dec;49:520–528. [PubMed: 15544981]
2. Heitkemper MM, Shaver JF, Mitchell E. Gastrointestinal symptoms and bowel patterns across the menstrual cycle in dysmenorrheic and non-dysmenorrheic women. *Nursing & Research in Health*. 1988; 37:108–113.
3. Whitehead W, Cheskin L, Heller B, et al. Evidence for exacerbation of irritable bowel syndrome during menses. *Gastroenterology*. 1990; 98:1485–1489. [PubMed: 2338190]
4. Heitkemper MM, Cain KC, Jarrett ME, et al. Relationship between bloating to other GI and menstrual symptoms in women with irritable bowel syndrome. *Dig Dis Sci*. 2004; 49:88–95. [PubMed: 14992441]
5. Kane SV, Sable K, Hanauer SB. The menstrual cycle and its effect on inflammatory bowel disease and irritable bowel syndrome: a prevalence study. *Am J Gastroenterol*. 1998; 93:1867–1872. [PubMed: 9772046]
6. Schmidt PJ, Nieman LK, Grover GN, Muller KL, Merriam GR, Rubinow DR. Lack of effect of induced menses on symptoms in women with premenstrual syndrome. *N Engl J Med*. 1991; 324:1174–1179. [PubMed: 2011161]
7. Andersch B, Milsom I. An epidemiologic study of young women with dysmenorrhea. *Am J Obstet Gynecol*. 1982; 144(6):655–660. [PubMed: 7137249]
8. Moos R. The development of a menstrual distress questionnaire. *Psychosomatic Medicine*. 1968; 30:853–567. [PubMed: 5749738]
9. Best WR, Beckett JM, Singleton JW, et al. Development of a Crohn's disease activity index. National Cooperative Crohn's Disease Study". *Gastroenterology*. 1976; 70:439–444. [PubMed: 1248701]
10. Harvey RF and Bradshaw MJ. Measuring Crohn's disease activity. *Lancet*. 1980; 1(8178):1134–1135.

11. Ware JE, Sherbourne CD. The MOS (medical outcome study) short form health survey (SF-36): Conceptual framework and item selection. *Med Care*. 1992; 30:473–483. [PubMed: 1593914]
12. Garratt AM, Ruta DA, Abdalla MI, et al. The SF-36 health survey questionnaire: An outcome measure suitable for routine use within the NHS? *BMJ*. 1993; 306:1440–1444. [PubMed: 8518640]
13. Guyatt G. A new measure of health status for clinical trials in inflammatory bowel disease. *Gastroenterology*. 1989; 96:804–810. [PubMed: 2644154]
14. Pullon S, Reinken J, Sparrow M. Prevalence of dysmenorrhea in Wellington women. *N Z Med J*. 1988; 101:52–54. [PubMed: 3380425]
15. Ng T, Tan N, Wansaicheong G. A prevalence study of dysmenorrhea in female residents aged 15–54 years in Clementi Town, Singapore. *Ann Acad Med Singap*. 1992; 21:323–327. [PubMed: 1416778]
16. Sundell G, Milsom I, Andersch B. Factors influencing the prevalence and severity of dysmenorrhea in young women. *Br J Obstet Gynaecol*. 1990; 97:588–594. [PubMed: 2390501]
17. Harlow S, Park M. A longitudinal study of risk factors for the occurrence, duration and severity of menstrual cramps in a cohort of college women. *Br J Obstet Gynaecol*. 1996; 103:1134–1142. [PubMed: 8917003]
18. Harel Z. Dysmenorrhea in adolescents and young adults: etiology and management. *J Pediatr Adolesc Gynecol*. 2006; 19:363e37. [PubMed: 17174824]
19. Neinstein, LS. *Adolescent Health Care: A Practical Guide*. Philadelphia: Lippincott Williams & Wilkins; 2002. pages
20. Rahbar N, Asgharzadeh N, Ghorbani R. Effect of omega-3 fatty acids on intensity of primary dysmenorrhea. *Int J Gynecol; Obstet*. 2012; 117:45.
21. Mirabi P, Dolatian M, Mojab F, et al. Effects of valerian on the severity and systemic manifestations of dysmenorrhea. *Int J Gynaecol Obstet*. 115(3):285–288. 211. [PubMed: 21959068]
22. Hendexi SL, Alesander NJ. Primary dysmenorrhea treatment with a desogestrel-containing low-dose oral contraceptive. *Contraception*. 2002; 66(6):393–399. [PubMed: 12499030]
23. Wyatt KM, Dimmock PW, Hayes-Gill B, et al. Menstrual symptometrics: a simple computer-aided method to quantify menstrual cycle disorders. *Fertil Steril*. 2002; 78:96–101. [PubMed: 12095497]
24. Willman EA, Collins WP, Clayton SG. Studies in the involvement of prostaglandins in uterine symptomatology and pathology. *Br J Obstet Gynaecol*. 1976; 83(5):337–341. [PubMed: 1268141]
25. Demers, LM.; Hahn, DW.; McGuire, JL. Newer concepts in dysmenorrhea research: leukotrienes and calcium channel blockers. In: Dawood, MY.; McGuire, JL.; Demers, LM., editors. *Premenstrual Syndrome and Dysmenorrhea*. London: Pitman; 1984. p. 205-213.
26. Chegini N, Rao CV. The presence of leukotriene C4- and prostacyclin-binding sites in nonpregnant human uterine tissue. *J Clin Endocrinol Metab*. 1988; 66:76–87. [PubMed: 2826530]
27. Akerlund M, Stromberg P, Forsling ML. Primary dysmenorrhoea and vasopressin. *Br J Obstet Gynaecol*. 1979; 86:484–487. [PubMed: 465399]
28. Akerlund M. Pathophysiology of dysmenorrhea. *Acta Obstet Gynecol Scand Suppl*. 1979; 87:27–32. [PubMed: 380250]
29. Bettendorf B, Shay S, Tu F. Dysmenorrhea: contemporary perspectives. *Obstet Gynecol Survey*. 2008; 63(9):597–603.
30. Parlak E, Dagli U, Alkim, et al. Pattern of gastrointestinal and psychosomatic symptoms across the menstrual cycle in women with inflammatory bowel disease. *Turk J Gastroenterol*. 2003; 14:250–256. [PubMed: 15048600]
31. Bernstein MT, Graff LA, Targownik LE, et al. Gastrointestinal symptoms before and during menses in women with IBD. *Alimen Pharmacol Therapeut*. 2012; 36:135–144. Hauser G, Tkalic M, Stimac D, et al. Gender related differences in quality of life and affective status in patients with inflammatory bowel disease. *Coll Antropol*. 2011; 35(Suppl 2):203–207. [PubMed: 22220436]
32. Hauser G, Tkalic M, Stimac D, et al. Gender related differences in quality of life and affective status in patients with inflammatory bowel disease. *Coll Antropol*. 2011; 352(Suppl 2):203–207. [PubMed: 22220436]

33. Felder JB, Korelitz BI, Rajapakse R, et al. Effects of nonsteroidal anti-inflammatory drugs on inflammatory bowel disease: a case-control study. *Am J Gastroenterol.* 2000; 95:1949–1954. [PubMed: 10950041]
34. Evans JMM, McMahon AD, Murray FE, et al. Non-steroidal anti-inflammatory drugs are associated with emergency admission to hospital for colitis due to inflammatory bowel disease. *Gut.* 1997; 40:619–622. [PubMed: 9203940]
35. Harel Z. Cyclooxygenase-2 Specific inhibitors in the treatment of dysmenorrhea. *J Pediatr Adolesc Gynecol.* 2004; 17:75–79. [PubMed: 15050982]

Table 1

Data collection

Data Element	Cases	Controls	Method of Collection		
			Interview	Self-completion of questionnaire	Medical record
Subject demographics	x	x	x		
Social habits	x	x	x		
Menstrual history	x	x	x		
Pregnancy history	x	x	x		
Dysmenorrhea screen	x	x	x		
Global pain severity [*]	x	x	x		
Hormone and other medication use over past 3 months	x	x	x		
Co-morbidities [†]	x	x	x		
Abdominal and pelvic surgery history	x	x	x		
Moos Menstrual Distress Questionnaire (MDQ)	x	x		x	
Short-Form 36 (SF-36)	x	x		x	
Crohn's disease location and behavior [‡]	x		x		x
Crohn's disease complications	x		x		x
Crohn's disease activity Index (CDAI)	x			x	x
Harvey Bradshaw Index	x			x	x
Inflammatory Bowel Disease Questionnaire	x			x	

^{*} Assessed with 0 to 10 scale where 0=no pain to 10=worst imaginable pain

[†] Includes endometriosis, polycystic ovarian syndrome, uterine fibroids, pelvic inflammatory disease, pelvic pain syndrome, cancer of the uterus, cervix, ovaries or vagina, interstitial cystitis, and fibromyalgia

[‡] As defined by Montreal classification

Such as small bowel obstruction, fistula or intra-abdominal perforation/abscess

Table 2

Demographics

Variable	Mean (SD)/Frequency		P
	Cases (N=54)	Controls (N = 66)	
Age	30.3 yr (8.40)	30.8 yr (8.58)	0.26
Race			0.34 *
White	52	60	
Black/African-American	1	1	
Asian	0	3	0.61 *
Ethnicity			
Not Hispanic or Latino	52	60	
Hispanic or Latino	1	2	
Other	0	1	0.47 *
Marital status			
Single, never married	22	32	
Divorced/separated	26	23	
Cohabiting	2	4	
Widowed	3	6	0.40 *
Highest degree obtained			
High school graduate	6	5	
Some college	20	15	
Associate degree	4	5	
Bachelor's degree	19	30	
Masters degree	4	9	0.23 *
Doctoral degree	0	1	
Occupation status			
Paid	34	42	
Unpaid/Volunteer	6	5	
Retired	1	1	0.34 *
Disabled	2	0	
Student	10	17	
Smoking status			
Never smoked	40	42	0.15 *
Former smoker	11	17	
Current smoker	2	6	
Alcohol use			0.15 *
Never drank	12	8	
Former drinker	4	2	
Current drinker	37	55	0.49 *
Marijuana use			

Variable	Mean (SD)/Frequency		P
	Cases (N=54)	Controls (N = 66)	
Never used	32	32	
Former user	17	27	
Current user	2	5	
Other illicit drug use			0.25 *
Never used	51	59	
Former user	1	5	
Current user	0	1	

* represents overall p-value for all groups in category

Table 3

Menstrual and pregnancy history

Variable	Mean (SD)/Frequency		P
	Cases (N=51)	Controls (N=65)	
Menarche (years)	13 (1.72)	13 (1.86)	0.42
Duration of cycle (days)	28 (1.9)	28 (2.1)	0.30
Duration of menses (days)	4.8 (0.7)	4.6 (0.6)	0.26
History of pregnancy	20	26	0.75
Number of live births	1.7 (1.0)	1.6 (1.2)	0.80

Table 4

Pain severity score and pain medication use

	Mean Pain Score (Range)	P	Any pain medication use for menstrual pain [‡]		P	NSAID use for any reason [‡]		P
			Y	N		Y	N	
Cases	Dysmenorrhea+ [*]	<0.001	17	4	0.001	10	11	0.405
	Dysmenorrhea– ^{**}		8	22		11	20	
Controls	Dysmenorrhea+	<0.001	26	4	NS	27	3	0.005
	Dysmenorrhea–		22	11		20	15	
Dysmenorrhea+ [*]	Cases	NS	17	4	NS	10	11	0.001
	Controls		26	4		27	3	
Dysmenorrhea– ^{**}	Cases	0.07	8	22	0.002	11	20	0.09
	Controls		22	11		20	5	

^{*} Dysmenorrhea+ = dysmenorrhea present^{**} Dysmenorrhea– = dysmenorrhea absent[‡] Includes NSAID and non-NSAID pain relievers[‡] Includes menstrual pain

Table 5

Menstrual distress scores

		Dysmenorrhea +	
		Cases (N=21)	Controls (N=30)
MDQ composite score	Mean (SD)	84 (88)	65 (52)
	<i>P</i>	NS	
MDQ pain score	Mean (SD)	19 (21)	13 (10)
	<i>P</i>	NS	
MDQ pain score (adjusted) *	Mean (SD)	19 (16)	13 (12)
	<i>P</i>	0.04 *	

MDQ = Menstrual Distress Questionnaire

* Adjusted for hormone, NSAID, and ASA use

Table 6

HRQOL scores (cases only)

Measure	Mean Score (SD)		<i>P</i>
	Dysmenorrhea + (N=21)	Dysmenorrhea– (N=32)	
MCS score	45 (10)	52 (6)	NS
PCS score	43 (10)	46 (9)	0.004
Total SF-36 score	89 (16)	98 (11)	0.016
IBDQ score	163 (33)	173 (33)	NS

SF-36 = Short-form 36; MCS = mental component summary; PCS= physical component summary; IBDQ = Inflammatory Bowel Disease Questionnaire