Turk J Gastroenterol 2003; 14 (4): 250-256

Pattern of gastrointestinal and psychosomatic symptoms across the menstrual cycle in women with inflammatory bowel disease

Inflamatuvar barsak hastalığı olan kadınlarda menstrüel siklus dönemlerinde gastrointestinal ve psikosomatik semptomlar

Erkan PARLAK, Ülkü DAĞLI, Canan ALKIM, Selçuk DİŞİBEYAZ, Bilge TUNÇ, Aysel ÜLKER, Burhan ŞAHİN

Türkiye Yüksek İhtisas Hospital, Department of Gastroenterology, Ankara

Background/aims: *The purpose of this study was to determine the frequency of defecation, gastrointestinal (GI) and non-GI symptoms among women with ulcerative colitis (UC) (n=38) and Crohn's disease (CD) (n=21), and to compare the results with those from healthy women (n=38) across the menstrual cycle.* ***Methods:*** *Women were followed for three menstrual cycles with a symptom diary consisting offrequency of defecation, and GI and non-GI symptoms. One point was allowed for each symptom in the same phases of three cycles, and total scores for GI and non-GI symptoms were obtained.* ***Results:*** *Frequency of defecation was found to be higher during menstruation in controls and in remitting UC and CD. GI symptom scores were higher in all three phases in patients with CD. These decreased in the postmenstrual phase in controls, and in patients with UC and remitting CD. In all three cycles, non-GI symptom scores were higher in patients with CD. These symptoms decreased during the postmenstrual period in all three groups. The activation of UC and CD did not affect the non-GI symptom score in the same menstrual cycle. Patients on mesalamine had less GI and non-GI complaints than those on sulfasalazine in all phases. There was no correlation between GI and non-GI symptom scores during all menstrual phases.* ***Conclusion:*** *Cyclic pattern present in healthy women persisted in patients with UC and CD. Disease activity and the drug used may modify the severity of the symptoms.*

Key words: Inflammatory bowel disease, ulcerative colitis, Crohn's disease, menstrual cycle

Amaç: *Bu çalışmanın amacı ülseratif kolit (ÜK) (n=38) ve Crohn Hastalığı (CH) olan (n=21) kadınlarda menstrüel siklus boyunca defekasyon sıklığını, gastrointestinal (GI) ve non-GI semptomları tesbit etmek ve sağlıklı kadınlarla (n=38) karşılaştırmaktır.* ***Yöntem:*** *Çalışmaya katılan kadınlar 3 menstrüel siklus boyunca defekasyon sıklığı, GI ve non-GI semptomları içeren semptom günlüğünü doldurdular. Her fazda herbir semptoma 1 puan verildi ve o faz için ortalama skorlar elde edildi.* ***Bulgular:*** *Defekasyon sıklığı kontrol grubu ile ÜK ve CH olan hastalarda menstürasyon sırasında daha fazla idi. CH olan hastalarda her üç fazda GI semptom skorları daha yüksekti. GI skorlar kontrollerde, ÜK'de ve remisyonda CH'nda postmenstrüel fazda azalıyordu. Her üç siklusta non-GI semptom skorları CH olan hastalarda daha yüksekti. Non GI semptom skorları her üç grupta da postmenstrüel periyodda azalıyordu. ÜK ve CH aktivasyonu GI semptom skorlarını etkilemiyordu. Mesalamin kullanan hastalarda GI ve non-GI semptomlar tüm fazlarda sülfazalazin alanlardan daha azdı. GI ve non-GI skorlar arasında menstrüel siklusun hiçbir fazında korelasyon yoktu.* ***Sonuç:*** *ÜK ve CH olan kadınlarda sağlıklı kadınlarda mevcut siklik pattern korunmaktadır. Hastalık aktivitesi ve kullanılan ilaçlar semptomların şiddetini değiştirebilir.*

Anahtar kelimeler: inflamatuvar barsak hastalıkları, ülseratif kolit, Crohn Hastalığı, menstrüel siklus

INTRODUCTION

Many women note gastrointestinal (GI) and systemic symptoms as well as a change in frequency of defecation across their menstrual cycle. Some studies on GI effects of sex hormones have revealed that GI transit time was longer in the luteal phase (1, 2), while others have found no difference in GI transit time among phases of the menstrual cycle (3-6). There were some studies showing that the form of the stool loosened during menstruation (6, 7); in others no difference was reported (3). It was also stated that women with dysmenorrhea had nausea, poor appetite, negative affective state, behavioral changes and autonomous reactions (7); women with functional abdominal pain (8) and irritable bowel syndrome (IBS) (9) had exacerbated GI symptoms during menstruation.

Address for correspondence: Erkan PARLAK
Türkiye Yüksek İhtisas Hospital, Department of Gastroenterology
06100, Yenişehir, Ankara, Turkey
Phone: +90 312 3103080
Fax: +90 312 3124122
E-mail: eparlak@ato.org.tr

Manuscript received: 08.07.2003 **Accepted:** 02.12.2003

Although there have been some studies on the relationship between GI and non-GI symptoms and the menstrual cycle in healthy women or in those with functional bowel disease, few studies have investigated this relationship in women with inflammatory bowel disease (IBD). Kane et al. (10), in their retrospective study, discovered that women with IBD had a higher prevalence of symptoms during menstruation than controls.

We therefore designed this prospective study to investigate whether there was any difference in frequency of defecation, or in GI and non-GI symptoms between healthy women and those with IBD, and also to determine the effects of disease activity and the drugs administered.

MATERIALS AND METHODS

Thirty-eight women with ulcerative colitis (UC) (34.5±8.9 years), 21 with Crohn's disease (CD) (38.1±8.2 years) and 38 women with no underlying disease (controls) (30.9±6.8 years) with regular periods were included in this study. Pregnant women and those taking oral contraceptives were excluded.

Criteria for the diagnosis of UC and CD were typical symptoms and physical signs supported by radiological and endoscopic features with compatible histological findings and operative features for CD. Patients with UC were classified into four groups according to endoscopic and radiological findings: an inflammatory process extending from just above the anal verge to the descending colon was defined as proctocolitis, inflammation extending to splenic flexure as left-sided colitis, that extending beyond the splenic flexure as extensive colitis and that involving the entire colon as pancolitis. Patients with CD were classified into three groups as ileitis, ileo-colitis and colitis. In patients with UC, the presence of active colitis determined clinically and endoscopically was defined as activation, while minimal bowel symptoms or absence of symptoms altogether with a healthy state endoscopically was defined as remission (11). For patients with CD, Crohn's Disease Activity Index above 150 was accepted as activation and below 150 as remission (12).

Women included in the study completed a form before going to bed every night containing questions on frequency of defecation, GI symptoms (poor appetite, nausea, vomiting, diarrhea, constipation, abdominal pain, abdominal distension and increased flatulence) and non-GI symptoms (irritability, nervousness, sleeplessness, restlessness, headache) covering the previous 24 hours for three cycles. They also indicated the dates of their period on the form.

To determine whether symptoms during menstruation were different from those at other times, data obtained during menstruation were compared with that obtained at premenstrual phase (for seven days before menstruation) and at postmenstrual phase (for seven days after menstruation).

To rule out daily or cyclic variations of symptoms, each symptom arising in the same phase of the three cycles were allocated one point and the median points were obtained; thus, total scores for GI and non-GI symptoms were determined. Furthermore, we investigated whether or not there was a correlation between scores for GI and non-GI symptoms and between activation of the disease and the drugs administered.

Statistical Analysis

For statistical analysis of patient age and the duration of the disease, one-way ANOVA was used, and for disease location, activation, and education level, chi-square test was used. To compare the frequency of defecation and scores for symptoms of active and remission period of each group obtained at each phase of the menstrual cycle, paired t test was used. One-way ANOVA test was used for comparison of symptoms arising in the same menstrual phases in patients with UC, with CD and in controls. To compare activation and remission of UC and CD, Student's t test was applied. Pearson moment product correlation analysis was done to determine whether there was a correlation between GI and non-GI symptom scores of the same cyclic period of each group.

RESULTS

The forms were given to 71 female patients with IBD and to 43 healthy women. Twelve (16.9%) patients and five (11.6%) controls were excluded from the study because of incorrect or incomplete answers ($p>0.05$). In total, data from 59 patients (38 UC and 21 CD) and 38 controls were evaluated. Characteristics of groups are shown in Table 1.

Frequency of defecation

While the frequency of defecation was found to be higher during menstruation than before and after

Table 1. General characteristics of women included in the study

	Ulcerative colitis (n = 38)	Crohn's disease (n = 21)	Controls (n = 38)	p
Age (yr)*	34.5±8.9	38.1±8.2	30.9±6.8	>0.05
Disease location, n (%)				
Distal	10 (26.3)	-	-	
Left	10 (26.3)	-	-	
Extensive	8 (21.1)			
Total	10 (26.3)	-	-	
Ileo-colitis	-	12(57.1)	-	
Colitis	-	9 (42.9)	-	
Age at the onset of the disease*	6.5±3.7	7.0±4.1	-	>0.05
Activation, n (%)				>0.05
Active	14 (36.8)	12 (57.1)	-	
Remission	24 (63.2)	9 (42.9)	-	
Education (yr)*	12.1±3.2	11.5±1.9	12.7±2.9	>0.05

*mean±SD

menstruation with patients with remission UC and in controls, this was observed to be much more during premenstrual period in active UC. In active UC, the frequency of defecation decreased during postmenstrual phase (Table 2). In active CD, frequency of defecation was high during the menstrual phase compared to premenstrual phase and there was no marked decrease in postmenstrual phase. Frequency of defecation was higher during menstruation than that of both premenstrual and postmenstrual phases during remission of the disease (Table 2).

Table 2. Frequency of defecation in phases of menstrual cycle

	Premenstrual (1)	Menstrual (2)	Postmenstrual (3)	1 vs 2	1 vs 3	2 vs 3
UC, n = 38	2.8±2.3	2.8±2.0	2.5±1.9	NS	<0.05	<0.001
CD, n = 21	2.9±1.4	3.3±1.3	3.2±1.6	<0.05	NS	NS
Controls, n =38	l.l±0.7	1.4±0.6	l.l±0.5	<0.001	NS	<0.001
p	<0.001	<0.001	<0.001			
UC-active, n = 14	5.1±2.3	4.9±1.7	4.2±2.1	NS	<0.001	<0.001
UC-remission, n= 24	1.4±0.8	1.7±0.8	1.5±0.7	<0.05	NS	NS
p	<0.001	<0.001	<0.001			
CD-active, n = 12	3.5±1.6	4.2±1.6	4.2±1.4	<0.05	<0.01	NS
CD-remission, n = 9	2.2±0.6	2.3±0.7	1.9±0.8	<0.05	<0.01	<0.01
p	<0.05	<0.001	<0.001			

: mean±SD; UC: Ulcerative colitis, CD: Crohn's disease

Gastrointestinal symptoms

Patients with UC and controls had more gastrointestinal complaints, especially abdominal pain, distension and flatulence, during menstruation than during both premenstrual and postmenstrual phases. Symptom scores in patients with CD did not change across the menstrual cycle and were higher in all three phases than in patients with UC and controls (Table 3). Poor appetite, diarrhea and abdominal pain were in particular responsible for this increase without considering cyclic variation. When the disease activity was taken into account, there were less symptoms in the postmenstrual phase than in premenstrual and menstrual phases in both active and remitting UC patients (Table 3). Patients with active CD had more GI complaints in all cycles but during remission of the disease, complaints decreased in the postmenstrual phase (Table 3).

Non-gastrointestinal symptoms

Patients with CD had a higher number of non-GI symptoms in all three cycles than those with UC and controls. Sleeplessness and restlessness accounted for this increase. Furthermore, there were

Table 3. Gastrointestinal symptom scores in phases of menstrual cycle*

	Premenstrual (1)	Menstrual (2)	Postmenstrual (3)	1 vs2	1 vs3	2 vs 3
UC, n =38	3.0±2.2	3.5±2.3	2.5±2.1	NS	<0.01	<0.001
CD, n = 21	3.5±2.4	3.6±2.2	3.3±2.6	NS	NS	NS
Controls, n =38	1.9±1.0	2.6±1.6	0.6±0.6	<0.001	<0.001	<0.001
P	<0.05	NS	<0.001			
UC-active, n = 14	4.8+1.9	4.7±2.3	3.9±2.3	NS	<0.05	<0.05
UC-remission, n = 28	1.9±1.5	2.7±2.1	1.6±1.4	NS	<0.01	<0.01
P	<0.001	<0.01	<0.01			
CD-active, n = 12	4.2±2.7	4.7±2.0	4.5±2.7	NS	NS	NS
CD-remission, n = 9	2.5±1.7	2.1±1.4	1.7±1.4	<0.01	<0.001	<0.001
P	<0.05	<0.01	<0.05			

*mean±SD

more non-GI symptoms in premenstrual and menstrual phases than in postmenstrual periods in all three groups (Table 4). The symptoms improving in postmenstrual phase were irritability, sleeplessness and restlessness. Women with active UC and CD and those in remission UC and CD showed similar scores for non-GI symptoms during the same menstrual cycle (Table 4).

Effects of drugs

Patients were taking either mesalamine (n=36) or sulfasalazine (n=23). In addition, two patients with UC (5.3%) and three with CD (14.3%) were receiving corticosteroids, and six patients with UC (15.8%) and three with CD (14.3%) were taking antibiotics (ciprofloxacin and metronidazole) ($p>0.05$). Patients on mesalamine had less non-GI complaints than those on sulfasalazine during premenstrual (1.9±1.4 vs. 2.3±1.6), menstrual (1.8±1.2 vs. 2.9±2.0) and postmenstrual phases (1.1+1.1.vs. 2.1±1.8) ($p<0.05$). In addition, patients on mesalamine had fewer GI complaints than those on sulfasalazine in premenstrual (2.7±2.3 vs. 4.0+2.0), menstrual (2.9±2.2 vs. 4.3±2.1) and postmenstrual phases (2.2±2.3 vs. 3.6±2.1) ($p<0.05$). The activation status of the patients according to the drugs they were taking did not differ between groups [14 patients with active disease were receiving mesalamine (38.8%) and 12 sulfasalzine (52.2%) ($p>0.05$)].

Although few patients (5) were receiving corticosteroids, these patients had a high number of GI and non-GI symptoms in all three cycles, but more symptoms in the premenstrual and menstrual phases than in the postmenstrual phase.

Nine patients on antibiotic therapy had more non-GI symptoms in the menstrual phase than those not receiving antibiotics (3.4±1.3 vs. 2.1±1.6) ($p<0.001$), but in other phases prevalence of symptoms was not high in these patients. There was a higher number of non-GI symptoms in the menstrual phase than in premenstrual (2.4±1.6) and postmenstrual phases (1.1±1.1) ($p<0.01$). Scores for GI symptoms in the menstrual phase were higher in patients receiving antibiotics than in those

Table 4. Non-gastrointestinal symptom scores in phases of menstrual cycle*

	Premenstrual (1)	Menstrual (2)	Postmenstrual (3)	vs2	vs3	2vs3
UC, n =38	1.7±1.3	1.8±1.5	1.1+1.2	NS	**<0.01**	<0.01
CD, n = 21	2.9±1.5	3.1±1.5	2.2+1.7	NS	NS	<0.01
Controls, n = 38	2.2±1.3	2.1±1.2	1.0±l.l	NS	<0.001	<0.001
P	<0.05	<Q.O1	<0.01			
UC-active, n = 14	2.1+1.2	1.8±1.8	0.8±0.9	NS	<0.001	<0.001
UC-remission,n =24	1.4±1.4	1.8±1.3	1.3±1.4	NS	NS	<0.001
NS	<0.001					
P	NS	NS	NS			
CD-active, n = 12	3.0±1.8	3.3±1.5	2.0±1.8	NS	NS	<0.05
CD-remission,n= 9	2.8±1.1	3.0±1.6	2.5±1.6	NS	NS	<0.001
P	NS	NS	NS .			

*mean±SD

not receiving antibiotics (5.7±1.7 vs.3.1±2.1) ($p<0.001$), but there was no difference in symptom score in other phases. The score was higher in the menstrual phase than in premenstrual (4.4±3.3) and postmenstrual phases (4.1±2.8) ($p<0.01$).

Patients receiving additional corticosteroids or additional antibiotics (double therapy) had more GI symptoms only in the menstrual phase than those receiving either mesalamine or sulfasalazine (1.8±1.5 vs. 3.1±1.5) ($p<0.01$). Patients on double therapy had as many non-GI symptoms in the menstrual phase as in premenstrual phase (2.7±l.-7), but they had more symptoms in postmenstrual phase (1.8±1.6) ($p<0.001$). GI complaints were high in all three menstrual phases: for monotherapy, while premenstrual, menstrual and postmenstrual values were 2.8±1.8, 2.8±2.1 and 2.2±1.8, for double therapy, these values were 4.3±2.7, *A.I±2.1* and 4.5±2.7, respectively. Patients on monotherapy had more GI symptoms during premenstrual and menstrual phases than in postmenstrual phase, while there was no difference in symptoms between menstrual phases in patients on double therapy.

Correlations

In controls, premenstrual and postmenstrual GI symptom scores were correlated with non-GI symptom scores, but menstrual scores were not correlated. In UC and CD, premenstrual and menstrual GI symptom scores were correlated with non-GI symptom scores, whereas there was no correlation between GI and non-GI symptom scores in postmenstrual phase (Table 5).

DISCUSSION

The results of this study demonstrate that there is a cyclic pattern related to menstruation in women with IBD and that the severity of symptoms and cyclic pattern can be influenced by the activation of the disease and the drugs employed.

Retrospective investigation via questioning of patients causes the symptom rate to be higher than expected. Our design, namely daily completion of forms, has prevented such a bias. Yet, there is a drawback in our design, which is partial completion of the form by some of the participants. Actually, it was observed that 16.9% of patients and 11.6% of the control group filled in the forms incompletely or incorrectly. In the present study, non-GI symptoms composed of psychoneurotic symptoms were not defined according to established scales for two reasons: 1. The consideration of so many symptomatological data could not be completely answered by the patients. 2. Many of the terms employed in these scales do not have corresponding meanings in our language. Therefore, a form consisting of simple symptom groups and which could be filled in daily during three cycles was developed. Another concern was that the patients might fill in the form in a haphazard way; however, the fact that data collected regarding the frequency of defecation and of the other GI symptoms were as expected rules out this probability to a large extent.

The fact that hormone levels were not measured may seem to be a limitation of our study. However, the hormone levels measured in women whose menstruation starts on the estimated day proved to be as expected. In fact, in GI transit studies on healthy women with regular periods, hormone levels estimated for the determination of menstrual phases yielded expected results (1-4).

There are few studies in the literature investigating the relation between menstrual cycle and IBD symptoms. In the study by Kane et.al. (10), diarrhea was found to be frequent in premenstrual phase in IBS and IBD patients compared to controls, and especially frequent in menstrual phase in CD and IBD. The correlations between disease activity and menstrual cycle in active and remitting UC were reported to be 65% and 38%, respectively, and the correlations between menstrual cycle and disease activity in active and remitting CD were 63% and 61%, respectively. In our study, GI symptoms and frequency of defecation were higher in UC and CD patients than in controls. The prevalence of GI symptoms in patients with remit-

Table 5. Correlations between gastrointestinal and non-gastrointestinal symptom scores in phases of menstrual cycle

	Ulcerative Colitis		Crohn's Disease		Controls	
	r	p	r	p	r	p
Premenstrual	0.5252	<0.001	0.8041	<0.001	0.5406	<0.001
Menstrual	0.5256	<0.001	0.8727	<0.001	0.1708	>0.05
Postmenstrual	0.3182	>0.05	0.3637	>0.05	0.6649	<0.001

ting disease was not much different from that of the control group. However, as the difference in symptoms between controls and patients with active disease was more pronounced, it is not surprising that in patients with bowel disease, frequency of defecation and GI symptoms were higher when compared to controls.

What must be explained here is the presence of a cyclic pattern. The reason for higher frequency of defecation during the menstrual phase may be an excessive prostaglandin release from the uterine cavity. However, as prostaglandins are metabolized rapidly, it is not known whether prostaglandin released from the uterus reaches the circulation and GI system (7, 13). Furthermore, in another study, endometrial prostaglandin levels were high in dysmenorrheic women. The fact that these did not describe changes in defecation pattern during menstruation does not support the above idea (14). A more probable mechanism is based on the fact that progesterone slows down GI transit time and is at its lowest levels during the menstrual phase. However, studies on this subject have yielded conflicting results. Wald et al. (1) showed that orocecal transit time was slower by 25% in luteal phase than in the follicular phase and emphasized its relation to progesterone. However, Hinds et al. (4) found that colonic transit time in the follicular phase was not different from that in the luteal phase. They speculated that colonic muscles were less sensitive to sex steroids. In another study, whole gut transit time was found to be no different in follicular and luteal phases. Frequency of defecation, stool form and stool weight were also not found to differ in follicular and luteal phases and during menstruation. The finding of long transit time in late pregnancy was claimed to result from high levels of progesterone (15). In conclusion, progesterone levels in the normal cycle do not have clinical importance (3). Heitkemper et al. (14) reported loosening in the form of the stool and increase in frequency of defecation during menstruation in healthy women.

We found in our study that the frequency of defecation and GI symptoms were similarly influenced by phases of the menstrual cycle. Frequency of defecation and GI symptom scores were high during menstruation in control patients. In both active and remitting UC, frequency of defecation and GI symptom scores were high during premenstrual and menstrual phases compared to postmenstrual phase, while in remitting CD, they were decreased in postmenstrual phase and in active CD they showed no cyclic pattern. We may speculate that inflammation in UC and CD counterbalances the effect produced by the mechanism of the cyclic pattern, while the effect of this control mechanism becomes apparent when the diseases are in remission.

The fact that high GI symptom scores were obtained for all cycles in patients on sulfasalazine, antibiotic and double therapy, but a cyclic pattern was maintained, suggests that the side effects of drugs given may contribute to GI symptoms and that increased drug number in particular may suppress the effects of the mechanism regulating the menstrual cycle.

Many studies have failed to show a relationship between hormone levels of ovaria and the psychological state. However, higher prevalence of these symptoms with concurrent lowest levels of progesterone emphasizes the decrease in serum progesterone level (16, 17). Kane et al. (10) reported high frequency of non-GI symptoms, especially irritability and headache, during menstruation in CD compared to controls and patients with UC or IBS.

Although scores for non-GI symptoms were highest during menstrual and premenstrual phases in controls, they decreased in postmenstrual phase (Table 4). Despite the increased scores for GI symptoms during menstruation, lack of correlation between scores for non-GI symptoms in healthy women (controls) (Table 5) suggests that non-GI symptoms may be brought about by changes in hormone levels independent of GI complaints. There are data in the literature supporting these findings. Whitehead et al. (9) found that exacerbation of bowel symptoms was not correlated with negative affect and behavioral changes during the menstrual cycle in women with IBS. The psychological states of women with IBS whose GI symptom scores increased during menstruation were found to be no different from those of the patients whose scores did not increase (18). Heitkemper et al. (14) did not find a correlation between psychopathological indicators and GI symptoms during menstruation.

Non-GI symptoms in patients with UC were comparable to those in controls (Table 4). The finding that GI symptoms were correlated with non-GI symptoms during premenstrual and menstrual phases but not during postmenstrual phase (i.e. while GI symptoms showed a significant decrease,

non-GI symptoms showed less significant decrease) (Table 5) suggests that GI symptoms are not responsible for development of non-GI symptoms. The similarity of non-GI symptom scores in active and remitting UC supports the above conclusion (Table 4).

Non-GI symptom scores in patients with CD were significantly higher than those in controls and patients with UC, a finding consistent with those of Kane et al. (Table 4). Despite absence of decrease in GI symptom scores, a fall in non-GI symptom scores in postmenstrual phase (Tables 3, 4) indicates effects of hormonal changes rather than those of GI symptoms. In fact, there was no correlation between GI and non-GI symptoms in postmenstrual phase (Table 5). Most probably these findings may be considered to reflect the difference in pathogenesis of CD from that of UC. This difference may result from some substances causing non-GI symptoms with high scores. While the mechanism typical of CD itself may contribute to effects of low levels of progesterone during premenstrual and menstrual phases in patients on corticosteroids and in those with UC, effects of hormones decrease in postmenstrual phase while effects of CD itself continue.

Although some of the patients with active UC were on corticosteroid or antibiotic therapy in addition to mesalamine or sulfasalazine, as in patients with CD, the finding that these patients had symptom scores similar to those of controls demonstrates that effects of drugs are not important in the development of non-GI symptoms.

In conclusion, the cyclic pattern present in healthy women is maintained in patients with IBD with respect to frequency of defecation and GI symptoms. IBD activity and drugs used may modify the severity of the symptoms and overshadow the effects of the cyclic pattern. Non-GI symptom scores were higher in patients with CD than in those with UC and in controls. Development of these symptoms is not influenced by GI symptoms, disease activity or the drugs used. The cyclic pattern, which is dependent on hormonal changes in healthy women, is not impaired in patients.

Further studies are needed to understand why non-GI symptom scores are higher in CD.

ACKNOWLEDGEMENT

I thank Kenan Kose for experienced statistical support.

REFERENCES

1. Wald A, Van Thiel DH, Hoechstetter L. et al. Gastrointestinal transit: the effect of the menstrual cycle. Gastroenterology 1981; 80: 1497-1500.
2. Davies GJ, Crowder M, Reid B. Et al. Bowel function measurements of individuals with different eating patterns. Gut 1986; 27: 164-9.
3. Kamm MA, Farthing MJG, Lennard-Jones JE. Bowel functions and transit rate during the menstrual cycle. Gut 1989; 30: 605-8.
4. Hinds JP, Stoney B, Wald A. Does gender or the menstrual cycle affect colonic transit? Am J Gastroenterol 1989; 84: 123-6.
5. Wyman JB, Heaton KW, Manning AP, Wicks AC. Variability of colonic function in healthy subjects. Gut 1978; 19: 146-50.
6. Turnbuil GK, Thompson DG, Day S, et al. Relationships between symptoms, menstrual cycle and orocaecal transit in normal and constipated women. Gut 1989; 30: 30-4.
7. Heitkemper MM, Shaver JF, Mitchell ES. Gastrointestinal symptoms and bowel patterns across the menstrual cycle in dysmenorrhea. Nurs Res 1988; 37: 108-13.
8. Heitkemper MM, Jarret M. Pattern of gastrointestinal and somatic symptoms across the menstrual cycle. Gastroenterology 1992; 102: 505-13.
9. Whitehead WE, Cheskin LJ, Heller BR, et al. Evidence of exacerbation of irritable bowel syndrome during menses. Gastroenterology 1990; 98: 1485-89.
10. 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: 1867-72.
11. Watts JM, de Dombal FT, Watkinson G, Goligher JC. Early course of ulcerative colitis. Gut 1966; 7: 16-31.
12. Best WR, Becktel JM, Singleton JW, Kem F. Development of a Crohn's disease activity index. National cooperative Crohn's disease study. Gastroenterology 1976; 70: 439-44.
13. Renaer M, Guzinski GM. Pain in gynecologic practice. Pain 1978; 5: 305-31.
14. Heitkemper M, Jarret M, Bond EF, Turner P. GI symptoms, function, and psychophysiological arousal in dysmenorrheic women. Nurs Res 1991; 40: 20-6.
15. Wald A, Van Thiel DH, Hoechstetter L, et al. Effect of pregnancy on gastrointestinal transit. Dig Dis Sci 1982; 27: 1015-8.
16. Laessle RG, Tuschl RJ, Schweiger U, Pirke KM. Mood changes and physical complaints during the normal menstrual cycle in healthy young women. Psychoneuroendocrinology 1990; 15: 131-8.
17. Abplanalp JM, Rose RM, Donnely AF, Livingston-Vaughan L. Psychoendocrinology of the menstrual cycle. II. The relationship between enjoyment of activities, moods, and reproductive hormones. Psychosom Med 1979; 41: 605-15.
18. Whitehead WE, Schuster MM. Gastrointestinal disorders: behavioral and physiological basis for treatment, San Diego: Academic, 1985: 155-77.