

## ORIGINAL ARTICLE

## The menstrual cycle affects rectal sensitivity in patients with irritable bowel syndrome but not healthy volunteers

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**Background:** We have previously shown that the menstrual cycle has no effect on rectal sensitivity of normal healthy women, despite them having looser stools at the time of menses. Patients with irritable bowel syndrome (IBS) often report significant exacerbation of their IBS symptoms with menses, raising the possibility that IBS patients may respond differently to the menstrual cycle.

**Aim and methods:** Rectal responses to balloon distension during days 1-4 (menses), 8-10 (follicular phase), 18-20 (luteal phase), and 24-28 (premenstrual phase) of the menstrual cycle were assessed in 29 female IBS patients (aged 21-44 years), diagnosed by the Rome I criteria. During the course of the study patients completed symptom diaries to assess abdominal pain and bloating (visual analogue scale), and frequency and consistency of bowel habits. In addition, levels of anxiety and depression were assessed using the hospital anxiety and depression questionnaire.

**Results:** Menses was associated with a worsening of abdominal pain and bloating compared with most other phases of the menstrual cycle ( $p < 0.05$ ). Bowel habits also became more frequent ( $p < 0.05$ ) and patients tended to have a lower general well being. Rectal sensitivity increased at menses compared with all other phases of the cycle ( $p < 0.05$ ). There was no associated change in rectal compliance, wall tension, or motility index. Neither was there any difference in resting anal pressure or the distension volumes required to relax the internal anal sphincter during the menstrual cycle.

**Conclusion:** These data (1) confirm that IBS symptomatology is exacerbated at menses and (2) show for the first time that in contrast with healthy women, rectal sensitivity changes with the menstrual cycle. These cyclical changes in sensitivity suggest that women with IBS respond differently to fluctuations in their sex hormonal environment or its consequences compared with healthy females.

In healthy women, stools are looser and more frequent at the time of menses but firmer during the luteal phase of the menstrual cycle.<sup>1-3</sup> This change in bowel habit may be related to cycling female sex hormones as high levels of progesterone and oestradiol, as seen during the luteal phase when stools are firmer, are associated with delayed gastrointestinal transit.<sup>2,4</sup> The menstrual cycle however does not appear to alter rectal motility or sensitivity in healthy women.<sup>3,5</sup>

Sex hormones may also play a role in the pathogenesis of irritable bowel syndrome (IBS). This is supported by observations that more women suffer from IBS than men,<sup>6,7</sup> and that premenopausal female patients often report exacerbation of their symptoms at the time of menses<sup>8-11</sup> and have fewer episodes of abdominal bloating than postmenopausal women.<sup>12</sup> Furthermore, postmenopausal women taking hormone replacement therapy (HRT) experience less bloating than those not taking HRT.<sup>12</sup> Men with IBS have also been shown to have lower levels of serum luteinising hormone than their unaffected counterparts.<sup>13</sup>

As patients with IBS, and in particular female patients, appear to have a hypersensitive/reactive gut to events such as mechanical distension,<sup>14,15</sup> food ingestion,<sup>16,17</sup> and stress,<sup>18</sup> the aim of this study was to assess whether they also respond differently from healthy women to the changing sex hormonal environment of the menstrual cycle. This was assessed by comparing rectal responses to balloon distension during days 1-4 (menses), 8-10 (follicular phase), 18-20 (luteal phase), and 24-28 (premenstrual) of the menstrual cycle in a group of female patients with IBS.

## MATERIALS AND METHODS

## Subjects

The studies were carried out on 29 female patients, aged 21-44 years (mean 35.2).

All subjects had symptoms that met the Rome criteria I for the diagnosis of IBS and had normal haematology, biochemistry, and sigmoidoscopy, together with a normal colonoscopy or barium enema if aged over 40 years. All women had a normal menstrual cycle (mean 27 days) and none described chronic gynaecological symptoms. None was taking any drug known to effect gastrointestinal motility and none was taking the oral contraceptive pill. All subjects gave informed consent and the study had local ethics committee approval.

## Protocol

Each woman was studied on four occasions: during days 1-4 (menses), 8-10 (follicular phase), 18-20 (luteal phase), and 24-28 (pre-menstrual phase) of their menstrual cycle, with day 1 being the first day of menstrual bleeding. The order in which the studies were carried out was randomised, and the studies were carried out at the same time of day.

Using a similar technique to that previously described to investigate anorectal physiology in healthy volunteers,<sup>3</sup> the subject was placed in the left lateral position and a multilumen polyvinyl catheter was inserted into the unprepared rectum. The catheter was positioned so that two side holes were in the rectum, 4.5 cm and 15.0 cm from the anal verge, and three side holes were in the anal sphincter, 0.5 cm, 1.0 cm, and 2.0 cm from the anal verge. Each side hole was perfused with water at a rate of 0.2 ml/min (Arndorfer Medical Specialties Inc., Greendale, Wisconsin, USA) and connected via water filled transducers to a polygraph recorder and visual display unit (Synectics Medical, Stockholm, Sweden). A

**Abbreviations:** IBS, irritable bowel syndrome; HRT, hormone replacement therapy;  $C_{\text{stat}}$ , static compliance;  $C_{\text{dyn}}$ , dynamic compliance.

**Table 1** Change in irritable bowel syndrome (IBS) symptomatology with the menstrual cycle

	Menses	Follicular	Luteal	Premenstrual
Pain	5.0 (3.9,6.2)	4.2 (3.0,5.3)	3.3 (2.1,4.6)	3.9 (2.9,5.0)
Mean difference		0.8 (0.1,1.7)*	1.7 (0.7,2.7)**	1.1 (0.5,1.7)**
Bloating	5.1 (3.7,6.4)	4.7 (3.4,6.0)	3.9 (2.5,5.3)	4.3 (3.2,5.4)
Mean difference		0.4 (-0.3,1.0)	1.2 (0.2,2.2)*	0.8 (0.03,1.5)*
Stool frequency	2.1 (0.3,7.3)	1.5 (0.3,3.7)	1.5 (0.3,10.0)	1.4 (0-4.0)
Median difference		0.6 (-0.7,3.6)**	0.6 (-7.5,2.3)**	0.7 (-0.6,3.3)**
Stool consistency	2.3 (2.0,2.6)	2.3 (1.9,2.6)	2.0 (1.6,2.3)	2.1 (1.8,2.3)
Mean difference		0 (-0.3,0.3)	0.3 (0.04,0.6)*	0.2 (-0.02,0.5)
General well being	5.2 (4.0,6.3)	6.1 (4.8,7.3)	6.3 (5.1,7.5)	5.6 (4.4,6.8)
Mean difference		-0.9 (-2.0,0.2)	-1.1 (-2.2,-0.1)*	-0.4 (-1.2,0.4)
Anxiety	10.6 (8.5,12.7)	10.9 (8.8,13.1)	10.9 (8.4,13.4)	10.2 (7.8,12.7)
Mean difference		-0.3 (-1.5,0.8)	-0.3 (-1.5,0.9)	0.4 (-1.2,1.9)
Depression	6.7 (4.8,8.6)	6.1 (4.5,7.7)	6.2 (4.1,8.2)	6.1 (4.4,7.8)
Mean difference		0.6 (-0.4,1.5)	0.5 (-0.7,1.7)	0.6 (-0.4,1.7)

Except for stool frequency, which is expressed as median [range], all other results are expressed as mean (95% confidence interval [CI]).

Mean/median difference is with respect to menses plus 95% CI/range, where \* $p < 0.05$  and \*\* $p < 0.01$ . Stool frequency is per day while stool consistency is based on a scale of 1-3 (1=hard, 2=normal and 3=loose).

6 cm latex balloon was attached to the tubing between 5 cm and 11 cm from the anal verge and the pressure within it measured using a water filled non-perfused channel, 8 cm from the anal verge. After a basal period of at least 10 minutes the latex balloon was serially inflated with air at 10, 20, 40, 60, 80, and 100 ml and then in 25 ml increments until the subject indicated discomfort. Each inflation was maintained for a period of one minute, followed by a period of complete deflation lasting at least one minute. During the procedure, patients were asked to mark on a standard form the nature of any sensation experienced (first sensation, desire to defecate, urgency, or discomfort). Although patients were informed of the nature of the sensations they might experience at the beginning of the study, they were not aware of the timing of the balloon distensions or prompted about the sensations during the studies.

Subjects were also asked to complete a symptom diary each day for the complete menstrual cycle indicating bowel frequency per day, stool consistency (based on a scale of 1-3 where 1=hard, 2=normal, and 3=loose), and the severity of their abdominal pain, abdominal bloating, and general well being using visual analogue scales (0-100 mm, 100 mm maximum). An assessment was also made of the subject's anxiety and depression using the hospital anxiety and depression questionnaire at each of the four visits.

### Analysis of data

The following measurements were derived from the anorectal study: (i) the lowest balloon volumes and pressures required for first sensation, and to induce sensations of desire to defecate, urgency, and discomfort; (ii) the steady state pressure in the rectal balloon at each distending volume and rectal compliance (calculated from both the volume/pressure relationship at 100 ml distension—static compliance " $C_{stat}$ "; and from the slope of the compliance curve—dynamic compliance " $C_{dyn}$ ")<sup>19</sup>; (iii) rectal motility index (calculated by summing the area under the rectal pressure profiles at 4.5 cm and at 15 cm); (iv) basal anal pressure; and (v) lowest distending volume required to initiate internal anal sphincter relaxation and to cause relaxation sustained throughout the distension.

Diary data for symptom severity were assessed from the visual analogue scales during the days of interest only. An average value over the days in question was then obtained (for example, menses: scores added from days 1 to 4 inclusive and divided by 4).

### Statistical analysis

All statistical analyses were performed using the hypothesis that symptom severity would be worst at the time of menses, as previously reported.<sup>8-11</sup>

Analysis was carried out using repeated measures analysis of variance (two tailed). Data were logged for physiological measurements to produce an adequate approximation to normal distribution. Friedman's test was used for the frequency data, followed by the Wilcoxon test where significant differences were observed.

## RESULTS

### Symptomatology

Both abdominal pain and bloating were significantly worse at menses compared with the luteal and premenstrual phases ( $p < 0.05$ ) (table 1). In addition, pain was greater at menses compared with the follicular phase ( $p < 0.05$ ) (table 1). Bowels were open significantly more frequently during menses compared with all other phases of the menstrual cycle ( $p < 0.05$ ) while stool consistency was harder during the luteal phase compared with menses ( $p < 0.05$ ) (table 1).

Furthermore, although there were no significant changes in levels of anxiety and depression with the menstrual cycle, there was a worsening in general well being at menses compared with the luteal phase ( $p < 0.05$ ) (table 1).

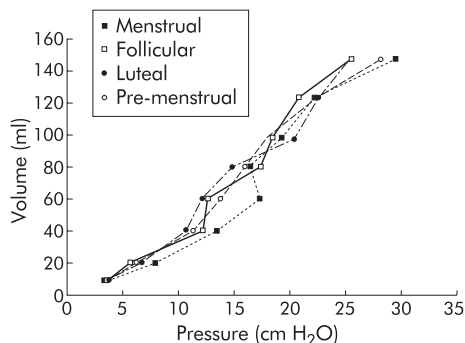
### Anorectal parameters

The distension volumes required to induce the sensations of "first sensation", "desire to defecate", "urgency", and "discomfort" were significantly lower during menses compared with most other phases of the menstrual cycle (table 2). Similarly, it can be seen from fig 1 that the pressure thresholds corresponding to each of the four volume thresholds were lower during menses compared with the other phases of the menstrual cycle, although these differences were not statistically significant. This increase in rectal sensitivity during menses was not related to any change in rectal compliance (change in  $dV/dP$  configuration or slope of curve), wall tension (change in  $C_{stat}$  without change in  $C_{dyn}$ ) (table 3, fig 1), or phasic activity (motility index) (table 3). Furthermore, there were no differences in resting anal pressure or distension volume required to relax the internal anal sphincter between the different phases of the menstrual cycle (table 3).

**Table 2** Change in rectal sensitivity (ml) with the menstrual cycle

	Menses	Follicular	Luteal	Premenstrual
1st sensation	10 (9, 10)	12 (10, 14)	12 (10, 14)	11 (10, 13)
Ratio		0.8 (0.7, 0.9)*	0.8 (0.7, 0.9)**	0.9 (0.7, 1.0)
Open bowels	22 (17, 29)	34 (26, 44)	34 (27, 43)	30 (23, 38)
Ratio		0.7 (0.5, 0.9)*	0.7 (0.5, 0.8)**	0.8 (0.6, 1.0)
Urgency	51 (39, 65)	71 (55, 91)	71 (55, 91)	75 (62, 90)
Ratio		0.7 (0.5, 0.9)*	0.7 (0.5, 0.9)*	0.7 (0.5, 0.9)**
Discomfort	117 (100, 136)	132 (116, 151)	133 (117, 152)	133 (117, 151)
Ratio		0.9 (0.8, 0.9)*	0.9 (0.8, 0.9)*	0.9 (0.8, 0.9)**

Results are expressed as geometric mean (95% confidence interval). Ratio is menses:period concerned, where \*p<0.05 and \*\*p<0.01.



**Figure 1** Relationship between mean balloon volume and pressure during the menstrual, follicular, luteal, and premenstrual phases of the menstrual cycle. Volume plotted up to a maximum of 150 ml as the number of subjects available for higher volumes was low (<4).

**Relationship between IBS symptomatology and rectal sensitivity**

The change in severity of any IBS symptom from either the follicular, luteal, or premenstrual phases to that during menses did not correlate with a corresponding change in sensitivity.

**DISCUSSION**

Our study has shown for the first time that in contrast with healthy females,<sup>3</sup> rectal sensitivity increases at the time of menses compared with all other phases of the menstrual cycle in female patients with IBS. Menses is also associated with a significant worsening of IBS symptomatology, which is in accordance with previous studies.<sup>8-11</sup>

Both abdominal pain and bloating were worse and bowel habits more frequent during menstruation. In addition, stool consistency was firmer during the luteal phase. Similar observations have been made in other studies<sup>8-11</sup> although one study reported no change in stool form or frequency with the menstrual cycle.<sup>10</sup> Furthermore, although general well being was reduced at menses, anxiety and depression remained unaltered throughout the menstrual cycle. This latter observation is in agreement with previous studies which have shown that psychological traits (including anxiety and depression) are not associated with perimenstrual bowel related symptoms.<sup>9 10 20</sup> Whether perimenstrual related symptoms may be associated with more subtle changes in mood and/or tension cannot be determined from this study but it might be expected that if gross changes in psychopathology are not associated with perimenstrual bowel related symptoms then more subtle changes in psychopathology are unlikely to be associated with these symptoms.

In contrast with our previous findings in healthy women,<sup>3</sup> rectal sensitivity at the time of menses was significantly increased with respect to all other phases of the menstrual cycle in females with IBS. This increase in rectal sensitivity did not correlate with the severity of any of the IBS symptoms. It has been shown that IBS patients can have altered visceral sensitivity throughout the gastrointestinal tract<sup>14 21 22</sup> and it is therefore possible that menses was associated with changes in sensitivity elsewhere in the gut which may be more closely correlated with IBS symptomatology. Furthermore, the increase in rectal sensitivity seen at menses does not appear to be related to changes in rectal compliance (change in dV/dP configuration or slope of curve) or wall tension (change in C<sub>stat</sub> without change in C<sub>dyn</sub>).

Previous studies have suggested that hard stools during the luteal phase of the menstrual cycle may be partly attributed to

**Table 3** Effect of the menstrual cycle on anorectal motility parameters

	Menses	Follicular	Luteal	Premenstrual
C <sub>stat</sub> (ml/cmH <sub>2</sub> O)	4.1 (2.0, 7.5)	3.3 (2.0, 5.1)	4.0 (2.4, 6.4)	4.2 (3.4, 5.0)
Ratio		1.2 (0.8, 1.7)	1.0 (0.4, 2.4)	1.0 (0.5, 2.1)
C <sub>dyn</sub> (ml/cmH <sub>2</sub> O)	0.53 (0.45, 0.61)	0.48 (0.39, 0.56)	0.53 (0.45, 0.62)	0.55 (0.47, 0.62)
Mean difference		0.06 (-0.14, 0.25)	0 (-0.14, 0.14)	-0.02 (-0.15, 0.12)
Motility index	759 (140, 4108)	686 (26, 17534)	780 (111, 5414)	516 (123, 2159)
Ratio		1.1 (0.2, 7.4)	1.0 (0.32, 3.0)	1.5 (0.7, 3.2)
Basal anal pressure (cm H <sub>2</sub> O)	76.1 (68.8, 84.2)	77.7 (72.0, 83.7)	79.2 (71.3, 88.0)	78.4 (71.9, 85.6)
Ratio		1.0 (0.9, 1.1)	1.0 (0.9, 1.0)	1.0 (0.9, 1.0)
Initial IAS relaxation (ml)	11.8 (10.5, 13.2)	11.8 (10.5, 13.2)	11.2 (10.1, 12.3)	12.7 (10.4, 15.3)
Ratio		1.0 (0.8, 1.2)	1.1 (0.9, 1.2)	0.9 (0.7, 1.1)
Sustained IAS relaxation (ml)	94.4 (70.2, 126.7)	86.2 (78.4, 94.8)	76.0 (54.9, 106.1)	78.9 (55.2, 112.6)
Ratio		1.1 (0.8, 1.6)	1.2 (0.7, 2.1)	1.2 (0.8, 1.7)

Results are expressed as geometric mean (95% confidence interval (CI)). Ratio is menses:period concerned. Mean difference is with respect to menses plus 95% CI. C<sub>stat</sub>, static compliance; C<sub>dyn</sub>, dynamic compliance; IAS, internal anal sphincter.

high levels of progesterone and oestradiol at that time,<sup>2,4</sup> and that diarrhoea reported at menses is related to prostaglandin production,<sup>23</sup> possibly by inhibiting transepithelial ion transport in the small intestine.<sup>24</sup> As an acute episode of diarrhoea induced by ingestion of an osmotic laxative is associated with an increase in rectal sensitivity in women (but not men),<sup>25</sup> and IBS patients seem to be more susceptible to sensitising events,<sup>14-18</sup> this may be the mechanism of the increased rectal sensitivity seen in IBS patients at menses. Alternatively, prostaglandins have been shown to induce afferent nerve sensitisation,<sup>26,27</sup> and as the gut of IBS patients may already be hypersensitive, prostaglandin release may be enough to trigger a further increase in this sensitivity. Another possibility is that we are detecting changes in vigilance during the menstrual cycle. We believe that this is unlikely as previous studies have shown that exacerbation of gastrointestinal symptoms at menses is not related to changes in psychopathology.<sup>9,10</sup> This is also supported by our observations that neither anxiety nor depression changed with the menstrual cycle.

Finally, no explicit statistical adjustments were made for the multiple comparisons performed in these studies but the relatively high proportion of significant results obtained probably excludes the possibility that these were obtained by chance. Furthermore, the use of a more conservative alpha level of 0.01 would not materially affect the results.

In conclusion, women with IBS appear to be predisposed to fluctuations in visceral sensitivity associated with the menstrual cycle. Understanding the pathogenesis behind these changes should help to unravel some of the mechanisms of visceral sensitisation.

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