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Meta-analysis: do irritable bowel syndrome symptoms vary between men and women?

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Abstract

Background—The aim of the study was to evaluate gender differences and the effect of menstrual cycle and menopausal status on irritable bowel syndrome (IBS) symptoms.

Methods—We performed a systematic review of MEDLINE to search for studies comparing IBS symptoms between gender, menstrual cycle phases, and menopausal states in IBS and/or healthy individuals. We performed meta-analyses to compare the relative risk (RR) of individual IBS symptoms between men and women.

Results—Twenty-two studies measured gender differences in IBS symptoms. Women were more likely to report abdominal pain (RR=1.12, CI [1.02, 1.22]) and constipation-related symptoms (RR=1.12, CI [1.02, 1.23]) than men (all $p<0.05$). However, men with IBS were more likely to report the diarrhea-related symptoms than women with IBS (RR=0.84, CI [0.75, 0.94], $p<0.05$). A systematic review of 13 studies demonstrated that both IBS and healthy women reported increased IBS symptoms during menses *vs.* other phases. There were insufficient data to determine the effect of menopause and hormone supplementation on IBS symptoms.

Conclusion—In the general and IBS populations, gender differences in IBS symptoms exist although these differences are modest. Studies suggest that female sex hormones influence the severity of IBS symptoms, but more studies are needed.

Keywords

irritable bowel syndrome; gender; abdominal pain; bloating; constipation; meta-analysis

INTRODUCTION

Irritable bowel syndrome (IBS) is characterized by recurrent abdominal pain or discomfort associated with a change in bowel habits.[1] The prevalence of IBS ranges from 6-22% in

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Mopelola Adeyemo has nothing to declare.
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Western countries, although the prevalence in Eastern countries tends to be lower and ranges from 2-17%.[2] IBS has a female predominance with a female-to-male ratio of 2-2.5:1 in those who seek health care. The female predominance is less apparent in the general population, which suggests that women with IBS are more likely to seek healthcare for their symptoms.[3-7] However, some Asian studies fail to report significant gender differences in the prevalence of IBS, suggesting that cultural differences may also play a role in IBS symptom reporting.[8, 9]

Gender differences in IBS are evident by sub-classification, non-gastrointestinal (GI) symptoms, pathophysiologic responses, and treatment response.[10] Specifically, female predominance is particularly apparent in the IBS with constipation (IBS-C) subtype compared to IBS with diarrhea (IBS-D) and alternating or mixed pattern (IBS-M).[11] Although gender differences in pathophysiologic studies (e.g., GI transit, rectal perception, brain activation patterns) have been reported in IBS and healthy controls,[12, 13] there are also conflicting reports that failed to identify differences between men and women.[14] Response to some IBS treatments, such as serotonergic agents, appears to be more robust in women than men.[12, 15-17] However, these findings may be due to an inadequate number of men in IBS studies rather than a true gender difference in non-study populations. In fact, there have been inadequate efforts to enroll sufficient numbers of men in many IBS studies and inadequate attempts to control for menstrual cycle phase among women in these trials.[10] In addition, gender differences and the effect of female sex hormones have largely been understudied in IBS. A recent review suggested that a strong relationship between menstrual cycle and bowel symptoms exists and that this may be due to effects of ovarian hormones on visceral pain sensitivity and bowel function.[18]

It is important to determine whether there are true symptom differences between genders in IBS because this information can potentially impact our understanding of the pathophysiology of IBS and influence research study design, drug development, and treatment. Two previous reviews assessed gender differences in the *diagnosis* of IBS. One review was conducted in developing countries,[19] while the other was a systematic review of studies conducted in community populations.[2] Both reviews concluded that most Western studies supported a female predominance of IBS. However, approximately half of the studies conducted in Eastern countries reported a female predominance while the other half did not. Irrespective of whether the studies were conducted in Western or Eastern populations, the female-to-male ratio was dependent on the diagnostic criteria, i.e., a greater female predominance was seen when Manning criteria was used vs. Rome criteria.[2]

In order to better understand gender differences in IBS, we performed a systematic review and meta-analysis of the literature to evaluate gender differences in *individual IBS symptoms* and the role of menstrual cycle, menopausal status and hormone supplementation on these symptoms. We hypothesized that the pooled data would reveal that women more frequently report abdominal pain and non-pain related symptoms associated with constipation such as hard stools, bloating, abdominal distension, and straining than men, and that men more often report symptoms associated with diarrhea such as loose stools and increased stool frequency. In addition, we hypothesized that the pooled data would reveal a higher prevalence of IBS symptoms at times when ovarian hormones are low, i.e. at the onset of menses in premenopausal women and during menopause, and these symptoms decrease with hormone supplementation.

METHODS

Search Strategy

The analysis for this study was based on a broader search for articles pertaining to dyspepsia and/or IBS. We conducted a comprehensive search for English-language studies in MEDLINE published up to June 2010, which examined gender differences in IBS and/or the effect of menstrual cycle, menopausal status, or hormone supplement on GI symptoms. The keywords and search strings used to perform the search with Reference Manager Software are indicated in Table 1. In addition, we performed manual searches of reference lists from relevant papers to identify other manuscripts which may have been missed by the search strategy.

Screening Strategy

We excluded titles if they did not meet the following inclusion criteria: (1) written in English, (2) investigation of humans, (3) examination of IBS or functional dyspepsia symptoms, (4) assessment of IBS or functional dyspepsia symptoms in relation to menstrual cycle, hormone supplement, and/or gender, and (5) study population consisted of the general population, and/or patient with dyspepsia and/or IBS. The analysis for this study was based on a broader search for articles pertaining to IBS and/or dyspepsia. Two reviewers then independently assessed the relevancy of the abstracts for the remaining articles. We excluded abstracts that did not meet these criteria. Next, the two reviewers independently assessed the manuscripts of the remaining abstracts based on the pre-specified inclusion criteria. Additionally, we manually reviewed the reference lists of identified studies to evaluate for extant literature not captured by the search strategy. In three cases, we contacted authors to obtain manuscripts. We applied Cohen's kappa statistic to assess inter-rater agreement and a third investigator resolved disagreements when necessary.

Data abstraction

We created a standardized data abstraction form in order to summarize information germane to the aims of this study. We compiled and summarized abstracted data using pre-specified evidence tables.

Quality Assessment (QA)

The Downs and Black (D&B) checklist was used to evaluate the quality of all studies (Appendix).[20] The D&B checklist was developed to assess the methodological quality of randomized and non-randomized studies of health interventions. Of the few checklists available that assess the quality of both non-randomized and randomized studies, the D&B checklist provides good test-retest reliability, inter-rater reliability, and criterion validity. Several systematic reviews and meta-analyses have used modified versions of this checklist to assess study quality.[21-23] The checklist is composed of 26 items subdivided into five components: reporting, internal validity, confounding, external validity, and power. Because 11 items in the original list were specific to randomized studies (intervention, randomization, and power calculation), these items were not included in the assessment of quality of non-randomized studies. The maximum QA score on the quality scales was 17 for non-randomized studies and 32 for randomized studies. In order to more effectively compare the quality of the studies we subjectively categorized the QA scores. For non-randomized studies, the quality was rated as poor, intermediate, and good if the QA score was 0-6, 7-11, and 12-17, respectively. For randomized studies, the quality was rated as poor, intermediate and good if the QA score was 0-10, 11-20, 21-32, respectively.

Statistical analysis

We performed statistical analysis only on those studies investigating gender differences in IBS symptoms, and performed meta-analysis only for IBS symptoms that were assessed in ≥ 3 studies. We reported summary statistics as relative risk (RR) favoring women. All data were fitted into a 2×2 matrix in order to calculate the summary effect using the Mantel-Haenszel Method. In cases where none of the subjects reported a particular symptom, 1.0 was added to each cell of the 2×2 matrix.

We used Cochrane's Q statistic to test for heterogeneity and adopted a P value of greater than 0.10 for the Q statistic as evidence for homogeneity.[24] If the data were homogeneous, we then selected a fixed-effects model.[24] If the data were heterogeneous, we then performed both a fixed and random-effects model.[24]

We performed a qualitative appraisal of publication bias by constructing a funnel plot and observing for evidence of asymmetry,[24] and performed a quantitative appraisal for publication bias by conducting an Egger's test.[24] We assumed there was evidence for publication bias if there was a qualitative lack of small “negative” studies on the funnel plot, or if the P value for the Egger's test was > 0.10.[24]

All statistical analysis was conducted using Stata™ statistical software version 8.0 (Stata Corp LP, College Station, TX, USA).

RESULTS

Of the 599 studies identified by the defined search strategy, 39 studies were included in our systematic review (Figure 1).[9, 25-60] There was sufficient inter-rater agreement among the studies selected (abstract κ=0.73 and content κ=0.83 selection).[61]

Gender differences in IBS symptoms

Table 2 shows the general characteristics of the 22 studies (9 surveyed the general population sample, 12 studied an IBS only sample, and 1 studied both general population and IBS) which compared prevalence rates of IBS symptoms in men and women.[9, 25-36, 47, 51-54, 56, 58-60] Fourteen studies were considered good quality and eight were considered of intermediate quality.

IBS diagnostic symptoms—In the general population, women were more likely to report abdominal pain and pain-related IBS diagnostic symptoms (Table 3, Figure 3).[27-29, 31, 34-36, 51, 58] In contrast, in the IBS patient population, the prevalence of the pain-related symptoms did not differ between men and women.

Supportive symptoms—Overall, women were more likely to report supportive symptoms of IBS than men (Table 3). In the general population, gender differences were seen in predominantly constipation-related symptoms including abdominal distension, bloating, and straining (Figure 3). The greatest gender disparities were seen with bloating and pain. Similarly, women with IBS demonstrated considerably higher risk for constipation-related symptoms including abdominal distension, bloating, infrequent stools and hard stools than men with IBS (Figure 4). Men with IBS were significantly more likely to report the diarrhea-related symptoms of loose/watery stools and increased stool frequency than women with IBS (Table 3).

Assessment for publication bias—Only two symptom comparisons surveyed in the general population showed a potential publication bias. Funnel plots suggest a lack of small,

positive studies for abdominal pain associated with change in stool frequency and a lack of small, negative studies for frequent stools.

Menstrual cycle effect on IBS symptoms

Table 4 provides general information on the 13 studies that assessed the effect of menstrual cycle on IBS symptoms.[32, 37-45, 62, 63] Study methodology varied with regards to study design and determination of menstrual cycle phase with seven studies of good quality and five of intermediate quality. Six studies assessed symptoms prospectively using daily diaries, one surveyed current symptom severity score, and the remaining studies used symptom recall. Only two studies used ovulation kits to document menstrual cycle phase.

All but three studies stated that women (average 40-60%) reported increased GI symptoms at time of menses compared to other phases.[32, 37-42, 44, 45, 62, 63] The symptoms for which most studies showed a significant menstrual cycle effect were (in descending order): loose stools, bloating, abdominal pain, stool frequency, and other changes in bowel habit (Figure 2, Table 4). In general, increased diarrhea was reported at the time of menses by more women than increased constipation. Although menstrual cycle effects on symptoms were similar in healthy women and IBS women, symptom severity was greater in women with IBS.

If only the seven higher quality studies were assessed, five reported a menstrual cycle effect on IBS symptoms at time of menses, while two did not. Bloating, gas and bowel habit changes (diarrhea more than constipation) were reported to increase at time of menses. Only 3 of these studies assessed symptoms prospectively and were from a single center.

Effect of menopausal status on IBS symptoms

Three retrospective and one prospective survey compared IBS symptoms in premenopausal vs. postmenopausal women[32, 37, 46, 55] and were considered to be of high quality. Sample sizes for premenopausal women ranged from 58-89 subjects and postmenopausal women ranged from 55-170 subjects. Amongst the three studies restricted to IBS,[32, 37, 55] nausea was the only symptom reported more frequently by premenopausal women than postmenopausal women.[32] In the study by Cain et al.,[55] various GI symptoms were reported less frequently by premenopausal women than postmenopausal women, however these differences were not significant after adjusting for age. Amongst healthy women, gaseousness and excessive flatulence were the only GI symptoms that were significantly more prevalent in postmenopausal women.

Effect of hormone supplementation on IBS symptoms

Table 5 shows the results from four studies which evaluated the effect of hormone supplementation on IBS symptoms in pre- or post-menopausal women. Two of the studies were randomized controlled trials; one evaluating the effect of estradiol or progesterone in postmenopausal women[50] was of high quality, and the other evaluating a gondotropin-releasing hormone (GnRH) agonist in premenopausal women[49] and was of intermediate quality. The other two studies were not randomized controlled trials. One consisted of a retrospective chart review[48] and the other was a prospective study,[39] but both achieved criteria for good quality.

Two studies investigated the effect of hormone replacement therapy (HRT) on IBS symptoms in women over the age of 50 who were presumably postmenopausal.[48, 50] Ruigomez et al.[48] found that women who use HRT are more likely to develop IBS than women who do not; however, the prevalence and severity of IBS symptoms were similar among non-HRT users and HRT users. Gonenne et al.[50] found that postmenopausal healthy

women who were given estradiol or progesterone therapy alone for 7 days were more likely to have looser stools and greater ease of passage than those on placebo.

Two studies evaluated the effect of hormone supplementation on IBS symptoms in premenopausal women. One study assessed the effect of oral contraceptive pills (OCP), while the other assessed the effect of a GnRH agonist.[38, 49] Heitkemper et al.[38] found that OCP use by women with IBS was associated with lower abdominal pain severity compared to non-OCP users but this difference did not maintain significance after correcting for multiple comparisons. Palomba et al.[49] found that treatment with a GnRH agonist improved the severity of IBS symptoms compared to placebo.

DISCUSSION

Due to conflicting data in the literature regarding gender differences in IBS, we performed a systematic review to investigate if there are differences in IBS symptoms between genders, and further evaluated the literature regarding the relationship between IBS symptoms, menstrual cycle phase, and menopause. Our study has four main findings: 1) women experience a greater prevalence of IBS symptoms than men, particularly constipation-related symptoms, 2) women appear to have more frequent and severe IBS symptoms during menses compared to other phases of the menstrual cycle, 3) the effect of hormonal therapy on IBS symptoms cannot be determined based on limited available data, and 4) there is a lack of studies comparing IBS symptoms in pre- and post-menopausal women.

For the most part, the occurrence and diagnosis of IBS is more common in women than men.[6, 29, 64] Female gender is a significant independent risk factor for the development of IBS,[65] including post-infectious IBS.[66] In cross-sectional surveys conducted in the U.S.,[67] Canada,[68] and Israel,[69] women reported IBS symptoms 1.5 to 2 times more commonly than men. Greater health care seeking and referral for IBS in women may in part be due to increased IBS severity[32, 70, 71] and greater impact of symptoms on health related quality of life in women with IBS compared to men.[70, 72, 73] However, population studies conducted in Asia suggest that the prevalence of IBS in men and women are similar.[19, 74-76] This difference may be largely due to cultural differences. In Asia, men see physicians as much and more often than women possibly for cultural and economic reasons.[76-79]

Gender differences in IBS symptoms

Our meta-analysis reveals that women more frequently report individual IBS symptoms than men. In general population studies, which included individuals with IBS, women reported a greater prevalence of the IBS diagnostic (i.e., pain-related) symptoms than men. These findings are consistent with studies which showed an enhanced perception of pain or discomfort to distension in the colon and rectum in women vs. men.[80, 81]

Overall, women had a greater prevalence of constipation-associated symptoms, particularly bloating and abdominal distension, associated than men. Men had a greater prevalence of diarrhea-associated symptoms of loose/watery stools and increased stool frequency in the IBS only studies, but not in the general population studies. This is in line with studies demonstrating a female predominance in IBS-C[67, 82, 83] and chronic constipation.[82, 84] Several studies have found that women have slower colonic transit than men.[85-87]

The generally higher IBS symptom reporting in women than men may be due to several reasons. Since women with IBS tend to have significantly more healthcare visits than men,[88] studies which used healthcare-based recruitment methods may underestimate the symptom prevalence in men. Another plausible explanation is that women tend to recall their symptoms better than men.[89] However, this is not likely to explain why constipation-

associated symptoms were reported more commonly in women than men, while diarrhea-associated symptoms were reported more often in men. Gender differences have been demonstrated in GI function, including transit time, visceral perception, brain activation patterns and colonic mucosal mast cell count[12, 13, 81, 90, 91] which can conceivably contribute to the greater prevalence of IBS symptoms in women and the gender differences in bowel habits.

The majority of Western studies reported a higher prevalence of individual IBS symptoms in women compared to men.[26, 27, 29, 30, 35, 36] Similarly, eight of the ten Eastern studies found that more women reported individual IBS symptoms than men,[9, 31, 33, 34, 51, 53, 56, 58] however one of these studies also reported higher prevalences of loose stools and increased stool frequency in men.[33] These studies were conducted mainly in community and university clinic populations, although one surveyed secondary clinic patients. Interestingly, two studies did not find a gender difference in individual symptoms but reported a higher ratio of women-to-men with Rome positive IBS (1.3-1.8:1).[25, 54] One of these studies was conducted in a rural community in Bangladesh[25] and the other in an urban community in Turkey.[54] Thus, this meta-analysis supports a higher overall prevalence of IBS symptoms in women than men in Western and Eastern countries although the differences are relatively modest. This review overcomes the limitations of previous epidemiological investigations,[9, 26-28, 30, 31, 33-36, 47, 92] because information from studies conducted in both Eastern and Western populations are included. However, additional studies are needed to investigate how the interactions between genetic, environmental and/or cultural factors contribute to gender differences in IBS symptoms and may differ across diverse cultures.

The relatively small, but significant gender differences in the prevalence of individual IBS symptoms suggests that gender effects may be confounded by other factors that significantly influence the presence of IBS symptoms. These include psychological and social factors that can affect symptom reporting, health care seeking and global outcomes in IBS.[93] For example, studies have reported that a previous history of abuse and other traumatic events or stressors are associated with more severe pain and greater symptom severity in IBS.[94-97]

Limitations of our meta-analysis include the extensive heterogeneity of the studies, which may in part explain the low RR estimates. For example, the diagnostic criteria used for IBS varied between studies. This is notable because gender differences in the prevalence of IBS vary according to criteria used.[98] In a population-based, cross-sectional survey study in Olmstead County, Minnesota, there was a greater prevalence of women with IBS if the Manning criteria were used, but a higher prevalence of men with IBS if the Rome criteria were used.[99]

Menstrual cycle effect on IBS symptoms

Our systematic review found that IBS symptoms are heightened at time of menses. Enhanced visceral perception at menses is supported by the finding of decreased sensory thresholds to rectal distension compared to other phases of the menstrual cycle.[40] One plausible mechanism that is supported by some animal and human studies is that declining or low ovarian hormone levels at time of menses may underlie the increased GI symptoms and discomfort across the menstrual cycle.[100] A study by Laessle and colleagues[101] showed that progesterone levels negatively correlated with pain-related symptoms (i.e., back pain and headache) which supports that lower levels of female sex hormones are associated with greater somatic pain. It is conceivable that women have more prevalent and severe IBS symptoms at time of menses when progesterone (and estrogen) decline from high to low levels. There are other possible mechanisms involved in GI function to explain these findings. For example, gender differences in post-prandial serotonin levels exist in IBS-D[102, 103] and in colonic mucosal mast cell counts in IBS.[91] Both have been found to

correlate with IBS symptoms and potentially a key role in the pathophysiology of IBS.[104] Additionally, mast cell secretion is affected by both estrogen and progesterone.[105]

While more studies reported increased diarrhea at time of menses than increased constipation, there were two retrospective recall studies which found that some women reported increased diarrhea and others reported increased constipation (Table 4).[42, 45] It is possible that an increase in a particular bowel habit would be reported by IBS patients with that predominant bowel subtype. For example, women with IBS-D may be more likely to report increased diarrhea than constipation, while IBS-C patients may be more likely to report increased constipation. However, this data was not available in the studies to determine if this could explain these findings.

Despite a relatively adequate number of studies, methodologic limitations in these studies could have affected the results. Half of the studies were based on symptom recall. Since women are likely to report a greater severity of symptoms retrospectively than prospectively,[106] the retrospective studies may overestimate the effect of menstrual cycle on IBS symptoms and are less accurate than prospective assessment. In addition, confirmation of menstrual cycle phase should be performed using ovulation kits although this was only done in two of the 12 studies. A review of the effect of menstrual cycle phase on experimental pain response found a lack of standardized operational definitions for identifying menstrual cycle phases.[107] More studies with an optimal study design (e.g., use of ovulation kits, prospective daily symptom assessment, sufficient sample sizes) are needed to truly assess the validity of the menstrual cycle effect on IBS symptoms.

Menopausal status effect on IBS symptoms

Due to the small number of studies that compared GI symptoms in pre- and post-menopausal women, there is insufficient evidence to determine the effect of menopausal status on IBS symptoms. However, the limited data suggest that premenopausal women with IBS are more likely to experience nausea than postmenopausal women with IBS. This finding is supported by studies which have shown that nausea and vomiting that occurred postoperatively,[108, 109] and during pregnancy,[110, 111] are associated with high levels estrogen and/or progesterone levels.

In one study, healthy post-menopausal women reported gas and excessive flatulence significantly more than pre-menopausal women.[46] To our knowledge, there have not been studies that have compared intestinal gas clearance or colon transit times in pre- and post-menopausal women.

Effect of hormone supplement on IBS symptoms

The available studies provided limited information and therefore a conclusion on the effects of hormone supplementation cannot be definitively determined. However, the available evidence suggests that use of OCPs and a GnRH agonist by premenopausal women may be protective of IBS symptoms, although further studies are needed. These medications act differently on the hypothalamic-pituitary-gonadal axis. OCPs prevent ovulation because the progesterone derivative inhibits the release of GnRH by the hypothalamus thereby decreasing the release of follicular stimulating hormone (FSH) and luteinizing hormone (LH) by the anterior pituitary, and estrogen inhibits follicular development. In contrast, leuprolide, the GnRH agonist, stimulates the release of FSH and LH, which suppress the secretion of ovarian hormones. Undoubtedly, more studies are needed to conclusively determine the effect of hormone supplements on IBS symptoms.

Conclusion

Our study demonstrates that women overall have a greater prevalence of IBS symptoms than men, particularly those associated with constipation. However, within the IBS patient group, men have more diarrhea symptoms than women. There are some limitations in the quality, methodology and number of studies evaluating the effect of menstrual cycle, hormone supplementation and menopausal status on IBS symptoms. Notably, most studies relied on symptom recall. Nonetheless, existing data raise the possibility that there may be a female sex hormone effect on IBS symptoms as well as on GI function. It is plausible that this may contribute to the increased prevalence and greater vulnerability to develop IBS, the higher prevalence of constipation symptoms, and the increased severity of symptoms at time of menses in women. In addition to the need for more, well-designed studies, there should be a greater attempt to recruit adequate and comparable numbers of men and women with and without IBS and attention should be paid to assessing and controlling for menstrual cycle phase and menopausal status in clinical study design since they can potentially affect study results.

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Appendix

Appendix

Down and Black checklist for measuring study quality.

Assessment	Scoring
Reporting	
1. Is the hypothesis/aim/objective of the study clearly described?	Yes=1 No=0
2. Are the main outcomes to be measured clearly described in the Introduction or Methods section?	Yes=1 No=0
3. Are the characteristics of the patients included in the study clearly described?	Yes=1 No=0
4. Are the interventions of interest clearly described?	Yes=1 No=0
5. Are the distributions of principal confounders in each group of subjects to be compared clearly described?	Yes =2 Partially=1 No =0
6. Are the main findings of the study clearly described?	Yes=1 No=0
7. Does the study provide estimates of the random variability in the data for the main outcomes?	Yes=1 No=0
8. Have all important adverse events that may be a consequence of the intervention been reported?	Yes=1 No=0
9. Have the characteristics of patients lost to follow-up been described?	Yes=1 No=0
10. Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?	Yes=1 No=0

Assessment	Scoring
Reporting	
External validity	
11. Were the subjects asked to participate in the study representative of the entire population from which they were recruited?	Yes=1 No=0 Unable to determine = 0
12. Were those subjects who were prepared to participate representative of the entire population from which they were recruited?	Yes=1 No=0 Unable to determine = 0
13. Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive?	Yes=1 No=0 Unable to determine = 0
Internal validity – bias	
14. Was an attempt made to blind study subjects to the intervention they have received?	Yes=1 No=0 Unable to determine = 0
15. Was an attempt made to blind those measuring the main outcomes of the intervention?	Yes=1 No=0 Unable to determine = 0
16. If any of the results of the study were based on “data dredging,” was this made clear?	Yes=1 No=0 Unable to determine = 0
17. In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls?	Yes=1 No=0 Unable to determine = 0
18. Were the statistical tests used to assess the main outcomes appropriate?	Yes=1 No=0 Unable to determine = 0
19. Was compliance with the intervention/s reliable?	Yes=1 No=0 Unable to determine = 0
20. Were the main outcome measures used accurate (valid and reliable)?	Yes=1 No=0 Unable to determine = 0
Internal validity-confounding (selection bias)	
21. Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?	Yes=1 No=0 Unable to determine = 0
22. Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time?	Yes=1 No=0 Unable to determine = 0
23. Were study subjects randomized to intervention groups?	Yes=1 No=0 Unable to determine = 0
24. Was the randomized intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?	Yes=1 No=0 Unable to determine = 0
25. Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?	Yes=1 No=0 Unable to determine = 0
26. Were losses of patients to follow-up taken into account?	Yes=1 No=0 Unable to determine = 0
Power	

Assessment	Scoring
Reporting	
27. Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%?	$<n_1$=0 n_1-n_2=1 n_3-n_4=2 n_5-n_6=3 n_7-n_8=4 n_8+=5

Abbreviations

IBS	irritable bowel syndrome
IBS-C	IBS with constipation
IBS-D	IBS with diarrhea
IBS-M	IBS with alternating bowel habits or mixed pattern
RR	relative risk
CI	confidence interval
QA	quality assessment
GnRH	gondotropin-releasing hormone
HRT	hormone replacement therapy
OCP	oral contraceptive agent
RCT	randomized controlled trial
1°	primary
2°	secondary
3°	tertiary
N/A	not applicable

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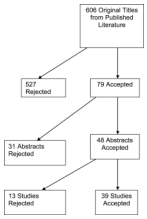

Figure 1.
Results of the literature search are shown.

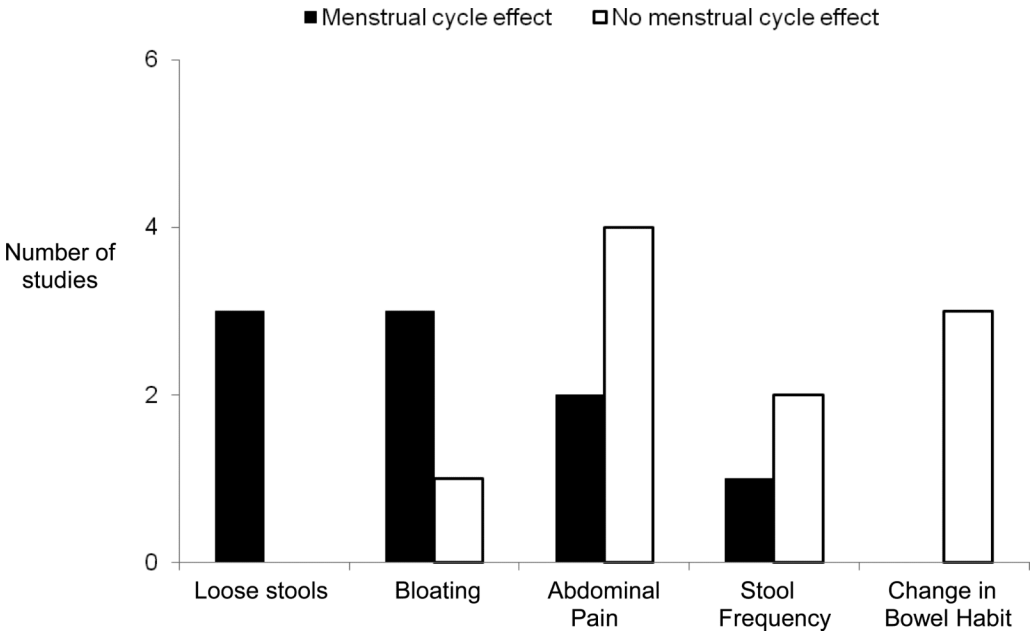

Figure 2.

The number of studies that tested for a significant effect of IBS symptoms on menstrual cycle is presented. The p-value of significance was specific to each study. One study was not included in the figure because statistical analysis of menstrual cycle effect on bloating was not performed.[37] Another study was not included because it did not specifically evaluate a menstrual cycle effect on these symptoms.[45]

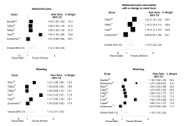

Figure 3.
Forest plots of the risk ratios and 95% confidence intervals for gender differences in general population studies evaluating abdominal pain, bloating, and straining are shown.

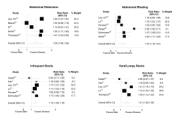

Figure 4.
Forest plots of the risk ratios and 95% confidence intervals for gender differences in IBS only studies evaluating bloating, distension, hard/lumpy stools, and infrequent stools are shown.

Table 1

Systematic review search strategy

Group	Search Terms	Significance of Grouping
1	MEDLINE	Targeted Bibliographic Database
2	Irritable bowel syndrome [MeSH Terms] OR irritable bowel OR gastrointestinal transit [MeSH Terms] OR intestinal transit OR functional gastrointestinal disorder* OR gastrointestinal motility [MeSH Terms] OR visceral hyperalgesia OR functional colonic diseases OR colonic diseases OR gastrointestinal diseases OR gastrointestinal transit OR intestinal pseudo-obstruction OR dyspepsia Field: title/ abstract	Targeted Topic Focus
3	Gender OR menstrual cycle [MeSH Terms] OR estrogen* OR progesterone [MeSH Terms] OR menstruation [MeSH Terms] OR luteal phase [MeSH Terms] OR oral contraceptives [MeSH Terms] OR testosterone [MeSH Terms] OR sex characteristics [MeSH Terms] OR sex hormones OR gonadal steroid hormones OR estradiol congeners OR contraceptive agents OR contraceptives, oral, hormonal [MeSH Terms] OR contraceptives, oral, sequential [MeSH Terms] OR contraceptives, oral [MeSH Terms] OR menopause Field: text word	Targeted Content Keywords
4	Review OR letter OR news OR editorial Field: Publication Type NOT Cat OR mouse OR rat OR feline OR porcine OR canine OR dog OR bovine OR cow OR horse Field: text word	Excluded study types and content

The four search groups were combined as follows: (1 AND 2 AND 3 NOT 4).

MeSH=medical subject heading. Asterisk (*) indicates keyword truncation

Table 2

Evidence table of studies comparing sex differences in IBS symptoms

Study	General Population N, (% F)	IBS N, (% F)	Population	Study Design	Setting	Country	IBS diagnostic criteria	QA
Bouchoucha[26]	134 (42.5)	752 (74.2)	IBS and Controls	Cross-sectional	2° Care	France	Rome I and II	11
Kim[51]	1717 (56.5)	N/A	General Population	Cross-sectional	University	Korea	N/A	15
Sandler[52]	2510 (62.0)	N/A	General population	Cross-sectional	N/A	USA	N/A	14
Shen[58]	491 (50.9)	N/A	General population	Cross-sectional	University	Chinese	N/A	8
Talley[27]	835 (54.0)	N/A	General population	Cross-sectional	N/A	USA	N/A	13
Talley[28]	726 (53.7)	N/A	General population	Cross-sectional	N/A	Australia	N/A	13
Tan[53]	533 (57.0)	N/A	General population	Cross-sectional	University	Malaysia	N/A	15
Taub[29]	1344 (61.6)	N/A	General population	Cross-sectional	N/A	USA	N/A	12
Tuteja[30]	723 (60.7)	N/A	General population	Cross-sectional	N/A	USA	N/A	15
Zuckerman[31]	405 (53.6)	N/A	General population	Cross-sectional	N/A	Vietnam	N/A	13
Celebi[54]	N/A	111 (64.0)	IBS	Cross-sectional	1° Care	Turkey	Rome II	15
Barakzai[47]	N/A	139 (71.4)	IBS	Retrospective	1° Care	USA (Mexican-Americans)	Rome II criteria met in 58% of women and 79% men	11
Han[9]	N/A	70 (45.7)	IBS	Cross-sectional	Community	Korea	Rome II	15
Lee, OY[32]	N/A	714 (66.8)	IBS	Cross-sectional	Advertisement and 3° Care	USA	Rome	13
Lu[33]	N/A	447 (40.5)	IBS	Cross-sectional	1° Care	China	Rome II	11
Masud[25]	N/A	593 (61.3)	IBS	Cross-sectional	Community	Bangladesh	Rome	13
Perveen[56]	N/A	116 (42.2)	IBS	Cross-sectional	Community	Bangladesh	Rome II	10
Ringel[60]	N/A	337 (70.9)	IBS	Cross-sectional	Community	USA	Modified Rome II	11
Schmulson[59]	N/A	295 (67.8)	IBS	Cross-sectional	Advertisement and 2° Care	Mexico	Rome II	11
Si[34]	None	662 (52.9)	IBS	Cross-sectional	2° Care	China	Rome II	15
Smith[35]	None	97 (62.9)	IBS	Prospective	2° Care	USA	Modified Manning	9

Study	General Population N, (% F)	IBS N, (% F)	Population	Study Design	Setting	Country	IBS diagnostic criteria	QA
Thompson[36]	None	156 (83.3)	IBS	Cross-sectional	1° and 2° Care	USA	90.4% met Manning criteria and 68.6% met Rome criteria	14

Abbreviations: QA: quality assessment; N/A: Not applicable; 1°: primary; 2°: secondary; 3°: tertiary

Table 3

Relative risk (RR) of IBS symptoms in women versus men in both the general and IBS patient populations

	General Population			IBS Only		
	RR favoring women (95% CI)	N of studies	Heterogeneity	RR favoring women (95% CI)	N of studies	Heterogeneity
IBS Diagnostic Symptoms						
Pain	1.12 (1.02,1.22)*	5	P<0.001	N/A	1	
Pain relieved with defecation	1.13 (0.97,1.31)	6	P<0.001	1.00 (0.80,1.25)	5	P=0.012
Pain associated with change in frequency	1.08 (1.03,1.14)*	6	P=0.005	N/A	1	
Pain associated with change in form	1.12 (1.02,1.23)*	6	P<0.001	0.96 (0.82,1.12)	4	P=0.69
Supportive Symptoms						
Distension	N/A	2		1.29 (1.06,1.56)*	5	P=0.002
Bloating	1.12 (1.01,1.25)*	9	P<0.001	1.37 (1.16,1.61)*	6	P=0.028
Incomplete Evacuation	1.03 (0.93,1.13)	6	P<0.001	1.15 (0.97,1.37)	7	P=0.300
Infrequent stools	1.06 (0.99,1.14)	5	P<0.001	1.13 (1.08,1.18)*	6	P=0.387
Lumpy/Hard stools	0.98 (0.88,1.10)	4	P<0.001	1.21 (1.08,1.36)*	5	P=0.089
Straining	1.12 (1.03,1.23)*	4	P<0.001	1.01 (0.93,1.09)	5	P=0.284
Mucus	1.02 (0.97,1.07)	5	P<0.001	1.07 (0.96,1.19)	8	P=0.002
Urgency	1.02 (0.93,1.11)	4	P<0.001	1.04 (0.95,1.15)	6	P=0.249
Loose/Watery stools	0.97 (0.92,1.01)	5	P=0.002	0.84 (0.75,0.94)*	5	P=0.420
Frequent stools	1.00 (0.98,1.01)	4	P=0.635	0.88 (0.80,0.96)*	5	P=0.014

Abbreviations: RR: relative risk; CI: confidence interval; N= number; N/A: Not applicable due to insufficient number of studies to perform meta-analysis.

*P < 0.05

Table 4

Evidence table of studies comparing menstrual cycle effect on IBS symptoms

Study	Population (N)	Study Design	Setting	Menstrual Cycle Assessment	IBS diagnostic criteria	Findings	QA
Jackson[41]	Healthy Controls (20)	Prospective (daily diary)	Not specified	Menses: day 1-4; Follicular: day 8-10 Luteal: day 18-20 Pre-menstrual: day 24-28	N/A	Stool form was significantly looser at menses compared to luteal phase; There was not a significant phase effect on number of stools per day	9
Hinds[62]	Healthy Controls (25)	Retrospective	Not specified	Recall	N/A	96% reported change in bowel habit before and during menses; 72% reported loose stools during menses; 32% reported constipation the week prior to menses	9
Simmons[44]	Healthy Controls (7)	Prospective (daily diary)	Not specified	Basal body temperature	N/A	No significant phase effect on stool form; 1 of 7 subjects reported constipation before or during menses; 2 of 7 subjects reported diarrhea at the beginning of menses	11
Lee, SY[43]	GI Clinic patients (193)	Cross-sectional (survey)	3° care	Menstrual: day 0-6; Proliferative: day 7-14; Secretory: after day 15	Rome II	50.8% of women met diagnostic criteria for IBS. No significant phase effect for abdominal pain, constipation, diarrhea, abdominal distension, tenesmus	13
Altman[63]	IBS (114)	Prospective (daily diary)	1° care and community	Menses: day 1; Luteal phase: 7-10 days prior to onset of menses	Diagnosis made by health care provider; criteria not specified	No significant phase effect on abdominal or stomach pain	13
Chang[37]	IBS (380)	Retrospective	3° care and community	Recall	Rome I	40% of bloating patients and 43% of bloating + distension patients reported that bloating was related to menstrual cycle	15
Houghton[40]	IBS (29)	Prospective (daily diary)	Not specified	Menses: day 1-4; Follicular: day 8-10; Luteal: day 18-20; Pre-menstrual: day 24-28	Rome I	There were significant phase effects on abdominal pain, bloating, stool frequency, and loose stools	11
Lee, OY[32]	IBS (477)	Retrospective	3° care and community	Recall	Rome	Overall 40% of women and 50.8% of women <45 yrs of age reported menstrual cycle-related worsening of symptoms	14
Heitkemper[38]	IBS (149) Healthy Controls (42)	Prospective (daily diary)	Community	Ovulation kit, Counting days	Rome I	Severity of bloating, and % days with loose stools (latter in IBS only) significantly increased during menses vs. other phases; No significant phase effect on abdominal pain, intestinal gas,	16

Study	Population (N)	Study Design	Setting	Menstrual Cycle Assessment	IBS diagnostic criteria	Findings	QA
						constipation, diarrhea, or hard stools	
Heitkemper[39]	IBS (44) Healthy Controls (25)	Prospective (daily diary)	Community	Ovulation kit	Rome	There was a significant phase effect on bloating and stool consistency; There was no phase effect on abdominal pain, intestinal gas, or stool frequency	15
Houghton[57]	IBS-D (39) Healthy Controls (19)	Cross-sectional	University clinic, general practices, advertiseme nt	Luteal phase (days 18-20 of cycle) or taking OCP were classified as High Progesterone/estrogen; Menses (days 2-3) was classified as Low Progesterone/estrogen: menses (days 2-3 of cycle)	Rome II	No differences in severity of pain, bloating, urgency, or overall symptoms between high and low progesterone/estrogen conditions in IBS-D women or healthy women.	11
Kane[42]	IBS (46) Healthy Controls (90)	Retrospective	2° care and community	Recall	Rome	Increased diarrhea was reported significantly more often during premenstrual period and menses in IBS vs. controls. Increased constipation was less often reported than diarrhea but was significantly more prevalent in IBS vs. controls during menses. There was a significant menstrual cycle effect on abdominal pain in IBS	16
Whitehead[45]	IBS (72) Healthy Controls (234)	Retrospective	1° and 2° care	Recall	Manning	IBS were more likely than controls to report menses-related increases in gas (39-48% vs. 14%), diarrhea (29-32% vs. 19%), and constipation (18-24% vs. 11%).	11

Abbreviations: QA: quality assessment; GI: Gastrointestinal; N/A: Not applicable; 1°: primary; 2°: secondary; 3°: tertiary; OCP: oral contraceptive agent

Table 5

Evidence table of studies comparing hormone supplement effect on IBS

Study	Treatment groups (N)	Population	Menopausal status	Study Design	Age (yrs)	Setting	IBS diagnostic criteria	Symptoms	QA
Ruigomez[48]	IBS HRT users (405); IBS HRT never users (255)	IBS	Not specified	Prospective	50 -69	1° care	Not specified	IBS symptoms were similar among users of HRT and HRT never users (data not provided)	15
Palomba[49]	Leuprolide acetate depot (LAD) plus tibolone (36); LAD plus placebo (37); Placebo (39)	IBS	Pre-menopausal	RCT	25.5 (mean)	2° care	Rome II	There was an improvement from baseline and vs. placebo in abdominal discomfort and distension, nausea, frequency and consistency, diarrhea, constipation, and bloating for both treatment groups	17
Gonenne[50]	Placebo (12), Progesterone (13), Estradiol (12), Combined progesterone and Estradiol (12)	Controls	Post-menopausal	RCT	40-65	Not specified	N/A	Treatment effect of looser stool consistency scores with progesterone alone, estradiol alone, and progesterone + estradiol; Greater ease of passage scores for estradiol alone; No treatment effect on stool frequency, stool consistency, or sense of incomplete passage	24
Heitkemper[38]	IBS oral contraceptive (56); IBS non-OCP (93)	IBS	Pre-menopausal	Prospective	32.5 (mean)	General population	Rome I	OCP users reported less severe abdominal pain than non-OCP users but this difference did not maintain significance after multiple comparisons. There were no significant differences in other individual GI symptoms.	16

Abbreviations: RCT: randomized controlled trial; 1°: primary; 2°: secondary; 3°: tertiary; HRT: hormone replacement therapy; OCP: oral contraceptive agent; N/A: not applicable