



The irritable bowel syndrome during pregnancy

William L. Hasler, MD*

*Associate Professor of Internal Medicine, Division of Gastroenterology,
University of Michigan Medical Center, Ann Arbor, MI, USA*

The irritable bowel syndrome (IBS) is characterized by altered bowel habits and abdominal discomfort in the absence of organic disease. No markers exist for IBS, and the definition of IBS is based on the presence of specific symptoms. The Rome II criteria for defining IBS include abdominal pain or discomfort for 12 weeks or longer, which need not be continuous, over the past 12 months plus two of the following: (1) relief of discomfort with defecation; (2) association of discomfort with altered stool frequency; and (3) association of discomfort with altered stool form [1]. Nine percent to 22% of the population report symptoms consistent with IBS. IBS is the most prevalent digestive disease, representing 12% of visits to primary care physicians, and 28% of referrals to gastroenterologists. Most cases of IBS present before 45 years of age.

In most Western societies, women develop IBS two to three times as often as do men. No investigations specifically have addressed the clinical features, epidemiology, or management of IBS in pregnancy. It is likely, however, to be prevalent in pregnant women, because so many patients with IBS are women of childbearing age. This article reviews what is known about the pathophysiology, symptomatology, epidemiology, and management of IBS during pregnancy.

Symptoms experienced in irritable bowel syndrome

IBS is a heterogeneous disorder with various clinical presentations. Patients with IBS report abdominal pain or discomfort on 33% of days, abdominal bloating on 28% of days, altered stool form on 25% of days, altered stool passage on 18% of days, and passage of mucus on 7% of days [2]. The intensity and location of the abdominal pain is highly variable. The

* 3912 Taubman Center, Box 0362, Ann Arbor, MI 48109.

E-mail address: whasler@umich.edu

pain is hypogastric in 25%, right-sided in 20%, left-sided in 20%, and epigastric in 10% of patients; it is described most commonly as crampy or achy. The abdominal pain may be exacerbated by meal ingestion, psychologic stress, or emotional turmoil. Constipation-predominant patients pass hard, pellet-like stools, whereas diarrhea-prone patients report frequent loose stools, often postprandially with urgency. Many patients alternate between diarrhea and constipation. Constipation- or diarrhea-predominant patients may note straining and a sense of incomplete evacuation at defecation. Half of patients have a mucoid discharge. Other symptoms are prominent. Heartburn, dyspepsia, early satiety, and nausea are experienced more than twice as often as in the general population. Genitourinary symptoms include pelvic pain, dysmenorrhea, dyspareunia, urinary frequency, nocturia, and a sense of incomplete bladder emptying. Musculoskeletal complaints are prominent, including low back pain, headaches, and chronic fatigue. IBS is associated strongly with fibromyalgia.

The symptoms of IBS appear to be prominent during pregnancy. Eleven to 38% of pregnant women report increased constipation, most often in the third trimester [3,4]. Conversely, 34% of women report increased stool frequency during pregnancy [4]. Circulating female sex hormones likely play important roles in the induction of gastrointestinal symptomatology in women. One third to 40% of healthy women experience gastrointestinal symptoms in association with their menses, whereas half of women with IBS experience an increase in their symptoms during their menses [5–8]. Gastrointestinal symptoms commonly experienced by women include gastrointestinal symptoms of abdominal bloating, constipation, abdominal pain, nausea, increased food sensitivity; women also experience non-gastrointestinal symptoms such as muscle stiffness [5,7].

Pathophysiology of irritable bowel syndrome

The pathogenesis of IBS is multifactorial, with contributions from abnormal gut motor and sensory activity, central nervous system (CNS) dysfunction, psychologic disturbances, genetic predisposition, enteric infection, and other luminal factors. Physiologic alterations associated with pregnancy may modulate these factors and affect the clinical manifestations of IBS.

Gastrointestinal motor abnormalities

Gastrointestinal motor abnormalities are common in IBS. Patients with IBS exhibit pronounced colonic responses to meal ingestion lasting up to three hours [9]. Patients with constipation-predominant IBS exhibit increases in the electric activity that produces segmenting colonic contractions that retard stool transit, whereas diarrhea-predominant patients exhibit reductions in this activity. Diarrhea-predominant patients with IBS have increased high-amplitude-propagated colonic contractions, the complexes that

precede defecation. In the small intestine, fasting contractile amplitude is blunted in constipation-predominant patients, whereas the duration of the stereotypic fasting pattern, the migrating motor complex (MMC), is shortened in diarrhea-predominant patients with IBS. In both constipation- and diarrhea-predominant patients with IBS, the duration of the fed intestinal motor pattern is shorter than in healthy volunteers. Small intestinal transit is delayed in constipation-predominant patients, but is accelerated in diarrhea-predominant patients. Sporadic motor patterns, including retrograde duodenal contractions, discrete clustered contractions, and prolonged ileal contractions, may occur more often in IBS than in healthy volunteers, but these are nonspecific findings. Extraintestinal smooth muscle may exhibit motor dysfunction. In IBS, the lower esophageal sphincter pressure is decreased, esophageal body peristalsis may be abnormal, gastric emptying of solids may be delayed, and tachygastria or bradygastria may occur. Gallbladder emptying and sphincter of Oddi function may be abnormal. Other smooth muscle abnormalities include detrusor instability of the bladder and airway hyperreactivity to methacholine.

Visceral sensory abnormalities

Abdominal sensation is mediated by afferent pathways activated by stimuli acting on chemoreceptors (which sense osmolarity, temperature, and pH), mechanoreceptors (which detect changes in tension), and mesenteric nociceptors. IBS is postulated to result from sensitization of visceral afferents so that physiologic events, not normally perceived by healthy individuals, induce pain in IBS. Indeed, patients with IBS can perceive physiologic small intestinal muscular contractions or experience pain during passage of food residue from the ileum to the cecum. Patients with IBS perceive exaggerated pain from colonic balloon inflation [10]. Patients with IBS experience heightened sensitivity to mucosal electric stimuli and to intestinal lipid perfusion; they also experience abnormal pain referral patterns during gut distention in that they can experience pain diffusely in the abdomen, back, shoulders, or chest. Patients with IBS who have hypersensitivity to rectal distention show heightened analgesic responses to the μ -opioid agent fentanyl, suggesting central opioid receptor dysfunction [11]. Whether or not the sensory dysfunction is generalized or limited to gut afferents is unknown. Some studies have reported similar responses to electric and thermal cutaneous stimulation in patients with IBS and healthy controls, but others have reported increased perception of cutaneous thermal pain in patients with IBS and heightened generalized somatic sensation in patients with IBS who have fibromyalgia.

Central nervous system dysfunction

IBS may be a primary gut disturbance with inappropriate CNS input or a primary CNS disorder with centrally directed changes in gut motor and

sensory function. Evoked potential recordings in patients with IBS exhibit decreased waveform latencies and increased amplitudes [12]. Using positron emission tomography (PET), patients with IBS demonstrate abnormal activation of regions of the brain, which mediate the affective components of pain perception and the supervision of visceral sensation, suggesting a primary central disturbance in processing of gut sensory information [13]. The presence of a pathogenic CNS defect is supported by the increased frequency of psychiatric abnormalities in IBS: the lifetime incidence of major depression, somatization disorder, generalized anxiety disorder, panic disorder, and phobias are higher in patients with IBS than in healthy controls. Increases in neuroticism, hostility, hypochondriasis, body pre-occupation, interpersonal sensitivity, concealed aggression, and introversion also are reported [14]. Psychiatric symptoms usually predate or occur simultaneously with the onset of bowel symptoms, indicating that emotional illness is not a result of IBS. Recent or remote emotional stress often triggers IBS symptoms. Sleep disturbances, including nocturnal awakening and awakening in the morning feeling unrested, occur in 72% of patients with IBS. Rates of severe lifetime sexual trauma, severe childhood sexual abuse, and any lifetime sexual victimization are significantly higher in patients with IBS than in individuals with inflammatory bowel disease [15].

Other pathogenic factors

Other contributing factors have been proposed. In a controversial recent study, 78% of patients had bacterial overgrowth based on hydrogen breath test responses to lactulose [16]. Some patients relate having gastrointestinal infection before developing IBS. Abnormal bowel function persists for more than six months after culture-proven bacterial gastroenteritis in approximately 25% of patients [17]. These patients have increased ileocecal mast cells, colonic mucosal enterochromaffin cells, CD3 lamina propria lymphocytes, and intraepithelial lymphocytes, which suggest a subtle inflammatory disorder in some cases of IBS. Some patients with IBS show a partial response to dietary exclusion of lactose, fructose, or sorbitol. True food intolerance is exceedingly rare. Several recent double-blind, placebo-challenge studies, however, identified offending foods in 6% to 58% of IBS cases, especially with diarrhea predominance [18].

Investigators have reported cholinergic dysfunction in constipation-predominant patients, adrenergic dysfunction in diarrhea-predominant patients, and abnormal release of various peptide hormones in selected patients. Serotonin (5-hydroxytryptamine, 5-HT) may play a pivotal pathogenic role. Diarrhea-predominant patients with IBS have increased postprandial plasma serotonin levels and increased numbers of serotonin-containing colonic epithelial cells [19]. Family members of patients with IBS often report bowel disturbances, suggesting a possible genetic component to the disorder. In one study, 4.8% of same-sex twins, including 186 monozygotic

and 157 dizygotic pairs, shared a functional bowel disorder [20]. Mathematic modeling indicated that 56.9% of the variance was attributable to genetic factors and 43.1% was attributable to environmental factors.

Irritable bowel syndrome pathogenesis in pregnancy

Pathogenic factors of IBS have not been studied rigorously in pregnancy. Hormonal and nonhormonal changes, however, during pregnancy modify gastrointestinal function.

Central nervous system factors in pregnancy

Several investigators have assessed psychologic function during pregnancy. Women develop anxiety disorders at approximately three times the rate of men. Panic disorder symptoms improved, however, in 41% and worsened in 38% of pregnant women in one study [21,22]. Depression and neuroticism likely are unaffected by pregnancy [23,24]. In contrast, pregnancy exacerbates obsessive-compulsive disorder and leads to increases in hypochondriacal behaviors and disease phobia [25–27]. Physical stress increases in the third trimester [28]. Although unstudied, the underlying emotional environment during pregnancy possibly may predispose to exacerbations of IBS.

Gender-related differences in gut function

Several investigators have documented gender-related differences in gut function, but the results are inconsistent. Colonic transit tends to be slower in women than men, but colonic transit time may not be related to the phase of the menstrual cycle [29]. Some investigators report prolongation of whole-gut transit during the luteal phase of the menstrual cycle, whereas others show no association [30–32]. Fasting small intestinal contractile amplitudes are increased and propagation velocities are slowed in women compared with men, whereas postprandial motor function is unaffected by gender [33]. MMC cycle duration correlates negatively with serum progesterone levels in the luteal phase. Gastric emptying tends to be slower and the postprandial increase in gastric slow wave amplitude, as measured by electrogastrography, is blunted in women [34–36]. The relation of gastric function to the menses is unclear: some studies show slowed emptying and reduced slow wave amplitude during the luteal phase and other studies show no effect [36–38].

Gender also may affect perception and central pain processing. Women (versus men) exhibited reduced thresholds to cutaneous stimulation, particularly during ovulation, suggesting gender-related and sex hormone-related increases in nociception [39]. Some preliminary investigations also show altered perception of colonic distention and of regional brain activation on PET scanning, although one study has reported no gender- or menses-related changes in rectal sensitivity [2,40].

Conversely, male sex hormones may protect against developing IBS. A trend of increased symptoms was observed in male patients with IBS who had low testosterone and luteinizing hormone (LH) levels. Sensory thresholds to rectal distention paradoxically correlated negatively with plasma testosterone levels, however, arguing against this conjecture [41].

A functional gastrointestinal disorder may affect circulating levels of sex steroids. In a study of women with severe constipation, progesterone and testosterone levels were reduced in the follicular phase of the menstrual cycle, whereas estradiol and testosterone levels were reduced in the luteal phase [42].

Gut function in pregnancy

Analysis of human gut function in pregnancy is restricted by the invasiveness of diagnostic tests; many tests employ ionizing radiation, which is teratogenic. Nevertheless, physiologic studies in humans and animal models have provided insight into gastrointestinal motor function during pregnancy. Using hydrogen breath test measurements after ingestion of nonabsorbable sugars, investigators have observed prolonged orocecal transit in women in the third trimester of pregnancy compared with the postpartum period (Fig. 1) [43,44]. In rats, small intestinal transit is retarded selectively in association with loss of the periodicity of fasting myoelectric

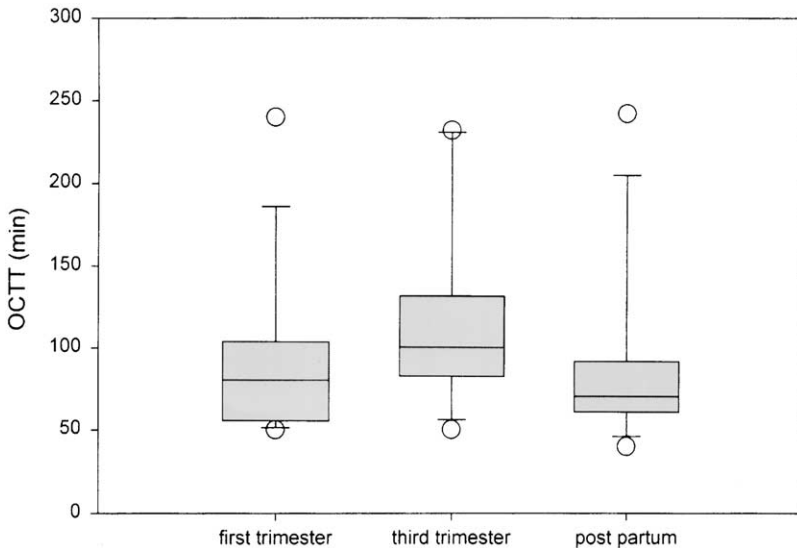


Fig. 1. Median values (*horizontal bar*) and 5th and 95th percentiles (*open circles*) of the orocecal transit time (OCTT) in the first trimester, third trimester, and postpartum period in 11 pregnant women are shown. OCTT increased significantly during the third trimester ($P < 0.05$), but returned to normal postpartum (From Chiloiro M, Carconza G, Piccioli E, et al. Gastric emptying and orocecal transit time in pregnancy. *J Gastroenterol* 2001;36:538–43; with permission.)

complexes [45,46]. Studies of gastric emptying in human pregnancy, as measured by acetaminophen absorption, have been contradictory: one study showed delays in the first trimester, but other studies showed no changes [47–49]. Slowed gastric emptying in pregnant guinea pigs is not associated with impaired smooth muscle responsiveness to acetylcholine, indicating that this effect of pregnancy does not result from impaired muscle contractility [50]. Retarded colonic transit in pregnant rats, however, parallels increases in nitric oxide synthase levels and production of cyclic guanosine monophosphate (GMP) in smooth muscle tissues, indicating that nitrergic nerve function increases during pregnancy [51].

Sex hormone effects on gut function

Pregnancy is associated with increased production of several hormones that affect gastrointestinal motor, myoelectric, and sensory function. Estrogen and progesterone increase throughout normal pregnancy. Administration of progesterone markedly increases gastrointestinal complaints in patients with functional bowel disorders [52]. Progesterone reduces the contractile force of smooth muscle in the canine colon and the murine jejunum [53,54]. The effects of progesterone on the stomach are controversial: some animal studies show acceleration of gastric emptying and others show delay; human studies show disruption of the gastric slow wave rhythm [55–57]. The effects of estrogen similarly are inconsistent: some animal studies show inhibition of gastric emptying; human studies show no effect on gastric function. Estrogen and progesterone synergistically cause degeneration of the gastric slow wave rhythm and delay colonic transit in rats [57,58]. These motor effects of estrogen and progesterone might increase the symptoms of IBS. Conversely, these hormones have analgesic properties that might reduce the pain of IBS. In rats, estrogen and progesterone administered in amounts that achieve the serum levels present in pregnancy produce opioid antinociception, antagonized by κ -opiate–receptor antagonists [59]. LH, produced midway through the menstrual cycle, and human chorionic gonadotropin (hCG), produced most prominently in the first trimester of pregnancy, bind to the same receptor. In rat small intestine, LH and hCG promote fragmentation and prolongation of the cycle length of the MMC [60]. Relaxin, a hormone produced after the tenth gestational week, produces relaxation of the cervix and symphysis pubis, increases ileal expression of nitric oxide synthases, and reduces ileal smooth muscle contractions in mice via increased nitrergic nerve activity (Fig. 2) [61].

Diagnostic approach for presumed irritable bowel syndrome during pregnancy

History and physical examination

Because IBS is a chronic disorder, many women already have an established diagnosis before conception. In these individuals, no further

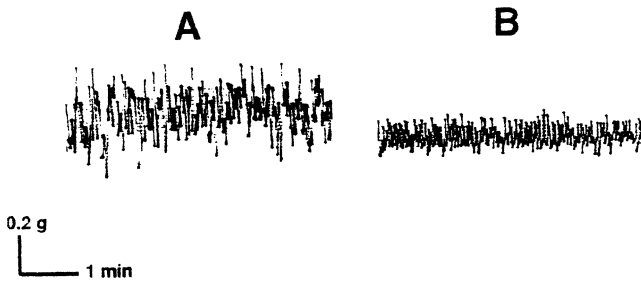


Fig. 2. Representative recordings of the force of spontaneous ileal muscular contractions, in grams of weight, versus time, in minutes, are shown in (A) control mice and (B) mice treated for 18 hours with relaxin. Relaxin markedly reduced ileal contractions (From Bani D, Baccari MC, Quattrone S, et al. Relaxin depresses small bowel motility through a nitric oxide-mediated mechanism. Studies in mice. *Biol Reproduction* 2002;66:778–84; with permission.)

diagnostic testing is indicated during pregnancy, unless their symptoms drastically change or alarm symptoms, such as bleeding, weight loss, or pyrexia, occur. When symptoms begin during pregnancy, IBS usually is reliably diagnosed by recognition of characteristic symptom profiles. In a questionnaire survey of nonpregnant individuals, Manning and colleagues identified the following symptoms as significantly more common in IBS than in organic disease: relief of abdominal pain upon defecation, looser stools with pain onset, more frequent stools with pain onset, and abdominal distention [62]. Ninety-one percent of patients with IBS had two or more of these symptoms versus 30% of those with organic disease. Kruis and coworkers found that absence of organic disease was predicted by (1) the combination of pain, flatulence, and irregular defecation; (2) symptoms persisting for more than two years; (3) pain described as burning, cutting, very strong, or terrible; (4) diarrhea alternating with constipation; (5) pencil-like or pellet-like stools; and (6) passage of mucus in stool [63]. More recently, the Rome I and II criteria have categorized more precisely the symptomatic patterns of IBS [1]. The accuracy of these symptomatic criteria has been assessed only in nonpregnant individuals. The Manning criteria have a sensitivity ranging from 58% to 90% and specificity of 74% to 87%, whereas the Kruis system has a sensitivity of 81% and specificity of 97%. In a prospective study, the positive predictive value of the Rome I criteria, in the absence of alarm findings, was 98% [64].

Physical examination of the pregnant woman with IBS usually is normal, except for the presence of the enlarged gravid uterus. Abdominal compression may elicit vague and poorly localized tenderness. Tender bowel loops may be palpated. Abdominal masses, hepatosplenomegaly, lymphadenopathy, ascites, blood in the stool, or autonomic or peripheral neuropathy are suggestive of organic disease and warrant further investigation.

Laboratory and structural findings in irritable bowel syndrome

Minimal laboratory evaluation and diagnostic testing are recommended for presumed new-onset case of IBS during pregnancy. Basic testing includes a complete blood count to assess for anemia, leukocytosis, or leukopenia; serum electrolytes; stool analysis for ova and parasites, bacterial pathogens, or *Giardia* antigen in the diarrhea-prone patient; an erythrocyte sedimentation rate as an indicator of inflammation; and thyroid chemistries to exclude thyroid dysfunction [65]. Recent studies suggest a possibly increased prevalence of celiac sprue in IBS; thus, determination of endomysial or tissue transglutaminase antibody status can be considered [66]. For diarrhea-predominant individuals, hydrogen breath testing, to exclude lactase deficiency, is recommended or an empiric dietary trial of lactose restriction if breath testing is unavailable. Sigmoidoscopy has been recommended for nonpregnant patients younger than 50 years old to exclude distal obstruction in patients with constipation and to exclude inflammatory diseases in patients with diarrhea [65]. In diarrhea-predominant patients, random colonic biopsies have been advocated to exclude microscopic colitis. The utility of many of these diagnostic tests in nonpregnant patients has been questioned. A study of patients satisfying the Rome I criteria found no diagnostic yield from the sedimentation rate, thyroid profile, and stool examination for ova and parasites in the absence of specific historical or examination findings. In two multicenter trials, lactose intolerance was diagnosed in 23% of patients, structural abnormalities were found in 2%, abnormal thyroid tests were observed in 6%, and ova and parasites were detected in feces in 2% [67]. The advisability of performing sigmoidoscopy in pregnancy to facilitate diagnosis of IBS is questionable. In a multicenter retrospective report of 48 sigmoidoscopies in 46 pregnant patients, sigmoidoscopy caused no complications, did not induce labor, and did not lead to fetal anomalies [68]. The indications for sigmoidoscopy, however, in this investigation included hematochezia in 29 patients, and the findings of sigmoidoscopy included ulcerative colitis in 12, Crohn's colitis in 8, pseudomembranous colitis in 1, and anastomotic ulcers in 1. This study population exhibited clinical presentations much more worrisome for organic disease than most individuals with presumed IBS. Even though diagnostic testing, including sigmoidoscopy, is generally safe in pregnancy, the clinician should weigh any potential benefits against the discomfort and anxiety such an evaluation produces. In many instances, testing can be deferred until postpartum.

Treatment of the pregnant woman with irritable bowel syndrome

The treatment of the pregnant woman with IBS ranges from patient education and dietary modifications to medications or psychologic intervention. Physicians should not rely on drugs that might have limited efficacy or unacceptable maternal or fetal side effects. Placebo response rates

from 30% to 70% have confounded the ability of controlled studies to detect benefits of drug therapy for IBS in nonpregnant patients. Few studies have addressed the management of IBS in pregnancy.

Dietary measures and fiber supplements in irritable bowel syndrome

Dietary modifications commonly are recommended in IBS. No controlled investigations of these interventions have, however, been performed during pregnancy. Dietary changes should play a prominent role in treating IBS during pregnancy because they usually are safe. Restriction of fat intake is reasonable because fat potently activates motor reflexes, such as the gastrocolic response. Patients with bloating and diarrhea should restrict intake of poorly digestible sugars, such as fructose and sorbitol. Diets that restrict selected foods according to the amount of gas produced have been advocated for patients with IBS who have bloating and excessive flatus.

Fiber supplements exhibit beneficial properties including enhanced fecal water retention, bulking of stool, formation of gels to provide stool lubrication, and binding potentially harmful bile acids. Bran accelerates colonic transit in healthy volunteers with relatively infrequent defecation, but retards transit in those with relatively frequent defecation. Psyllium reduces the perception of rectal distention, indicating that fiber may also improve visceral afferent function. In a meta-analysis, bran increased fecal weight in 18 of 20 studies and accelerated fecal transit in 16 of the studies [69]. Soluble fiber, such as pectin, psyllium, or oat bran, enhances fecal water retention, whereas insoluble fiber, such as cellulose or lignin, more effectively enhances fecal bulk.

Fiber supplements, including bran, psyllium, processed flea seed husk (ispaghula), and calcium polycarbophil, have been analyzed in placebo-controlled studies in patients with IBS. Many investigators report increases in stool weight, decreases in colonic transit time, and improvement in constipation, but most investigators observe no improvement in patients with diarrhea- or pain-predominant IBS. Different fiber preparations may have different effects on specific symptoms. Bran increases abdominal distention and flatulence, whereas processed preparations, such as psyllium, reduce these symptoms [70].

Pregnant women with constipation do not eat less fiber than pregnant women without constipation [71]. Nevertheless, corn biscuits or wheat bran supplementation increases stool frequency and improves stool consistency in constipated pregnant patients (Fig. 3) [72]. Fiber supplementation thus should be considered a first-line therapy for constipation-predominant IBS during pregnancy.

Medications for irritable bowel syndrome

Drug recommendations for IBS during pregnancy must weigh carefully the expected therapeutic gain versus the fetal risk. Although IBS adversely

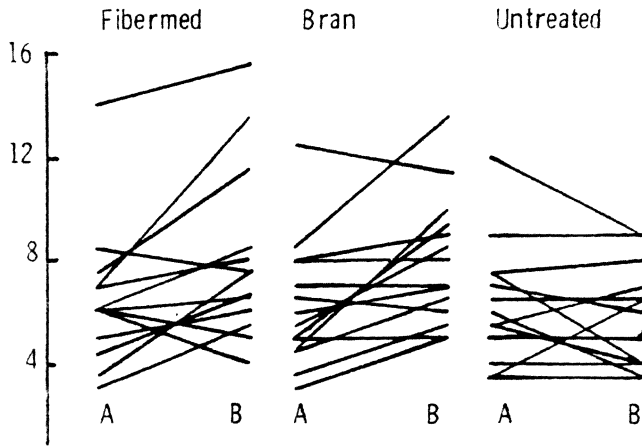


Fig. 3. The number of bowel movements per week is shown before (A) and during (B) fiber supplementation with a corn biscuit (Fibermed), bran, or placebo. Both fiber preparations increased stool frequency but the placebo produced no effect (*From Anderson AS, Whicelow MJ. Constipation during pregnancy: dietary fiber intake and the effect of fiber supplementation. Human Nutr Appl Nutr* 1985;39:202–7; with permission.)

affects quality of life, it does not produce significant physical debilitation. Thus, the clinician should rely more on reassurance, dietary modification, and psychologic intervention and less on drugs in pregnant than non-pregnant women. Initiation of a new medication during pregnancy should be performed with obstetric consultation.

Prescription drugs are categorized by the Food and Drug Administration (FDA) according to safety during pregnancy. Most agents used to treat IBS are category B—animal studies do not show risks to the fetus and there are no controlled human studies, or animal studies show adverse effects but human studies show no risk to the fetus; category C—animal studies show teratogenic or embryocidal effects but there are no human studies, or there are no animal or human studies in pregnancy; or category D—positive evidence of human fetal risk exists but benefits in certain situations may make the drug acceptable despite the risks. Although imperfect, this classification helps assess the risks versus benefits of medications in the pregnant woman with IBS.

Laxatives

Osmotic laxatives often are recommended for patients with constipation-predominant IBS who do not respond to fiber. These agents accelerate colonic transit and increase stool frequency in patients with idiopathic slow transit constipation. Osmotic laxatives include hypertonic salt solutions such as milk of magnesia, poorly absorbable sugars such as lactulose and sorbitol, and isotonic electrolyte solutions containing polyethylene glycol.

Few studies have analyzed the efficacy of laxatives for constipation during pregnancy. In a study of 62 pregnant patients, lactulose increased stool frequency from 2.5 to 4.0 per week after one week of therapy and normalized stool frequency and consistency after two weeks [73]. The safety of laxative treatment in pregnancy is well analyzed: docusate, bisacodyl, senna, cascara, and phenolphthalein probably are safe if used infrequently [74]. Danthron, another anthraquinone stimulant, possibly is teratogenic [75]. Hypertonic saline laxatives should be used with caution, because they can cause maternal sodium retention and electrolyte disturbances [76]. Isotonic electrolyte solutions with polyethylene glycol have not been studied in pregnancy but probably are not teratogenic, as they are not absorbed and do not cause significant fluid shifts (FDA category C). Castor oil should not be used because it stimulates uterine contractions. Mineral oil should not be administered orally because it can impair maternal fat-soluble vitamin absorption, leading to neonatal coagulopathy and hemorrhage [74].

Antidiarrheal agents

Peripherally acting opioid agents are the initial therapy of choice for nonpregnant patients with IBS who have diarrhea [65]. These agents increase segmenting colonic contractions, delay fecal transit, increase anal pressure, and reduce rectal perception of pain. Placebo-controlled investigations of loperamide in nonpregnant patients report decreased stool frequency and urgency, improved stool consistency, reduced borborygmi, and improved sense of well being in patients with diarrhea or diarrhea alternating with constipation. Bile-acid sequestering drugs and acid-suppressing medications also have been proposed to treat diarrhea in patients with IBS.

Few studies have assessed the safety of antidiarrheal treatments during pregnancy. In a study of 105 women administered loperamide (FDA category B) during pregnancy, the rate of fetal malformations, spontaneous abortions, or premature births was not increased, although 21 women had babies 200 grams smaller than a matched control group [77]. Thus, infrequent use of this drug during pregnancy probably is safe. In contrast, diphenoxylate with atropine is associated with fetal anomalies in animals and humans and should be avoided (FDA category C) [78]. Cholestyramine, a bile acid-binding agent, has been used to treat cholestasis of pregnancy without complications, but can produce manifestations of fat-soluble vitamin deficiency, including coagulopathy (FDA category C) [79]. This potentially could cause fetal or neonatal intracerebral hemorrhage. Clotting function and levels of fat-soluble vitamins must be monitored during chronic use in pregnancy. Kaolin and pectin are not absorbed and probably are safe, although kaolin-impaired iron absorption has been reported [80].

Antispasmodic agents

Antispasmodic drugs are the most commonly prescribed agents for IBS. They are the initial recommended therapy for nonpregnant patients with IBS

who have severe pain [65]. This category includes anticholinergic agents, calcium channel blockers, direct gut smooth muscle relaxants, and agents that act via unknown pathways. In a meta-analysis of 26 double-blind trials, antispasmodic agents produced greater global improvement and pain reduction than placebo (62% versus 35% and 64% versus 45%, respectively), although none of the drugs analyzed (cimetropium, pinaverium, trimebutine, octylonium, and mebeverine) is approved in the United States [81]. A second meta-analysis of controlled trials of cimetropium, hyoscine, mebeverine, otylonium, pinaverium, and trimebutine reported superior global improvement and pain reduction in the antispasmodic group [82].

Anticholinergic agents are the most commonly prescribed antispasmodics in the United States. In small clinical trials, dicyclomine, prifinium, and cimetropium ameliorated the symptoms of IBS. Calcium channel blockers have been proposed to treat IBS because of an antispasmodic action. In a double-blind trial, diltiazem did not produce global improvement, but tended to reduce diarrhea and abdominal pain. In a randomized, placebo-controlled trial, pinaverium reduced the duration of abdominal pain. In a placebo-controlled trial of 325 patients, octylonium significantly reduced the number of pain episodes, reduced abdominal distention, and improved the global assessment [21]. A meta-analysis of eight randomized, controlled trials of peppermint oil reported a trend toward therapeutic benefit in IBS, but this could not be definitively concluded because of methodologic concerns [83].

No studies have assessed the efficacy of antispasmodics for IBS during pregnancy, although several studies have examined their safety. Dicyclomine has been associated with phocomelia (FDA category B) [84]. With the antihistamine doxylamine, dicyclomine was a component of the drugs Bendectin and Debendox, which were removed from the market because of concerns about teratogenicity. Several studies reported an increase in genital tract abnormalities, limb defects, and congenital heart disease from Bendectin, whereas other studies reported no increase in malformations [85–88]. The risk of hyoscyamine in pregnancy is unexplored (FDA category C). Because of these concerns, anticholinergic antispasmodics should not be prescribed routinely but reserved for refractory pain from IBS during pregnancy. Calcium channel blockers, such as nifedipine or diltiazem, have not been associated with increases in congenital abnormalities (FDA category C), but should be used with caution during pregnancy because they can cause maternal hypotension [89].

Antidepressant agents

Tricyclic antidepressants have clear efficacy in selected nonpregnant patients with IBS. Amitriptyline produces benefits in global well being, abdominal pain, and bowel habits, whereas trimipramine ameliorates vomiting, depression, insomnia, and fecal mucus and sometimes reduces abdominal pain. Desipramine decreases abdominal pain, stool frequency, and depression in diarrhea-prone patients.

The efficacy of other classes of antidepressants is less clear. The selective serotonin reuptake inhibitor (SSRI) paroxetine accelerates orocecal transit, suggesting possible use in constipation-predominant patients. The SSRI citalopram blunts perception of rectal distention and reduces the magnitude of the gastrocolic response in healthy volunteers [90]. In a small placebo-controlled study, citalopram reduced abdominal pain in IBS [91]. A meta-analysis of tricyclic and nontricyclic antidepressants reported an odds ratio for clinical improvement of 4.2 (confidence interval 2.3–7.9) [92]. A meta-analysis of all antidepressant trials in IBS reported an odds ratio for improvement in abdominal pain of 8.0 and for global improvement of 4.4 [93].

The safety of antidepressant drugs during pregnancy has been studied extensively for the treatment of depression but not for the treatment of IBS. In one study, women who became pregnant on tricyclic antidepressants, women who were prescribed tricyclics while pregnant, and women who refused tricyclic antidepressants during pregnancy exhibited no significant differences in the rate of fetal malformations or pregnancy complications, although neonates whose mothers had taken tricyclic antidepressants during pregnancy had short-term neonatal withdrawal symptoms of cyanosis, respiratory distress, irritability, autonomic dysfunction, and hypoactivity [94,95]. Cases of neonatal heart failure and electrocardiographic abnormalities also have been reported [89]. In one investigation, fluoxetine tended to cause an increased rate of miscarriage, but this finding was not confirmed in a recent meta-analysis [96,97]. A study of 267 women on newer SSRIs reported no increase in fetal malformations, miscarriage, prematurity, or low-birth-weight infants [98]. Intrauterine SSRI exposure also causes a neonatal withdrawal syndrome consisting of irritability, crying, shivering, increased tonus, difficulty eating, insomnia, and seizures [99]. Maternal use of tricyclics or SSRIs during pregnancy does not affect global intelligence quotients, language, or behavioral development of their children assessed at the preschool level (Table 1) [100]. In women receiving these two classes of antidepressants, symptoms need to be monitored as the dose requirement progressively increases during pregnancy [101,102]. Tricyclic agents are listed either as FDA category C (desipramine and amitriptyline) or D (nortriptyline and imipramine); whereas SSRIs, such as fluoxetine, paroxetine, sertraline, and citalopram, are FDA category C. These drugs should be considered only for severe gastrointestinal symptoms of IBS during pregnancy.

Other medications for irritable bowel syndrome

Several agents reduce gas and bloating from IBS, but these agents have not been studied during pregnancy. In uncontrolled studies, simethicone reduced excess bloating and flatus. Activated charcoal has a large surface area to mass ratio (450 to 1800 m²/g) and is an excellent adsorbent of gas. Studies have shown variable reduction of gaseous symptoms with activated

Table 1

Results of neurobehavioral tests in infants according to exposure in utero to antidepressant drugs^a

| Test ^b | Score | | | Adjusted differences (95% CI) ^c | |
|--|--|------------------------|---------------------|---|---------------------------|
| | Tricyclic antidepressant drugs (N = 80) | Fluoxetine (N = 55) | Control (N = 84) | Tricyclic antidepressant drugs vs. control | Fluoxetine vs. control |
| Bayley Mental Development Index | 118 ± 17 | 117 ± 17 | 115 ± 14 | 2.4 (−4.5 to 9.4) | 2.1 (−5.0 to 9.2) |
| McCarthy General Cognitive Index | 117 ± 10 | 114 ± 16 | 114 ± 13 | 2.7 (−2.3 to 7.6) | 4.7 (−4.0 to 13.4) |
| Reynell Verbal Comprehension Scale | 1.3 ± 0.8 | 1.2 ± 1.2 | 1.1 ± 0.9 | 0.3 (−0.1 to 0.5) | 0.3 (−0.1 to 0.6) |
| Reynell Expressive Language Scale | 0.3 ± 0.9 | −0.2 ± 1.0 | 0.1 ± 1.0 | 0 (−0.3 to 0.3) | −0.1 (−0.4 to 0.3) |

^a Plus-minus values are means ± SD.

^b The children were tested between 16 and 86 months of age (mean, 33 ± 14). The Bayley and McCarthy scores are typical for this age. The normal range for both rests is 100 ± 1 SD. Lower scores mean lower cognitive function. The mean Reynell score in normal children of this age is 0 ± 1 (range of possible scores, −3 to +3).

^c Multiple regression analysis was used after adjustment for children's age; maternal IQ, socioeconomic status, score on the Center for Epidemiologic Studies Depressed Mood Scale, and score on the Global Assessment Scale; and duration of exposure to drug (first trimester vs. entire pregnancy). CI denotes confidence interval.

From Nulman I, Rovet J, Stewart DE, et al. Neurodevelopment of children exposed in utero to antidepressant drugs. *New Engl J Med* 1997;336:258–62; with permission.

charcoal. The microbial α -galactosidase agent Beano reduces hydrogen production after black bean ingestion by healthy volunteers. In a controlled trial, pancreatic enzymes reduced bloating, gas, and fullness after healthy volunteers ate a high-fat, high calorie meal [103]. Beano or pancreatic enzymes have not been investigated in IBS.

Based on a hypothesized role of food allergy, IBS has been treated with mast cell degranulation inhibitors. In uncontrolled studies, sodium cromoglycate reduced symptoms in patients with diarrhea-predominant IBS and dietary hypersensitivity, but these studies require confirmation in a placebo-controlled study. In a study of 481 pregnant women, sodium cromoglycate did not increase the rate of congenital malformations (FDA category B) [104].

Tranquilizers have been used for decades to treat IBS. Older studies reported benefits for phenaglycodol, meprobamate, heteronium plus amobarbital, propantheline plus phenobarbital, chlordiazepoxide, diazepam, medazepam, and aprazolam. Many of these studies, however, were small or poorly designed. Anxiolytics are not recommended for most patients with IBS

because of the potential for drug abuse or tolerance. This is true especially in pregnancy: benzodiazepines, including diazepam, aprazolam, and lorazepam, can lead to major fetal malformations, cleft lip, respiratory depression, and low Apgar scores at birth and functional deficits and behavioral problems during child development (FDA category D) [105,106].

Psychologic therapy of irritable bowel syndrome

Psychologic therapies are reserved for patients with IBS who have psychosocial features that fail to respond to standard therapy. A comprehensive review identified only 14 well-designed, controlled studies of psychologic treatments published between 1966 and 1994 [107]. Eight of the studies reported that psychologic treatment was superior to control treatment, but six reported no benefit. Because of methodologic inadequacies, the efficacy of psychologic therapy in IBS is not established. Promising forms of psychotherapy for IBS include dynamically oriented psychotherapy, group psychotherapy, and psychodrama. Cognitive therapy produces long-term, persistent improvements in bowel symptoms. A recent trial reported superior responses and improved quality of life when a multi-component program, consisting of IBS education, muscle relaxation, cognitive coping strategies, and assertiveness training, was added to standard therapy, compared with standard therapy alone [108]. Muscle relaxation training and education reduce bowel symptoms, including abdominal pain, flatulence, eructation, and bloating in some studies. Hypnosis decreases abdominal pain, abdominal distention, nausea, and flatulence; regularizes bowel habits; and improves overall well being. These effects are sustained for up to 18 months [109]. The pregnant patient with IBS may be considered for psychologic therapy for severe symptoms because of concern about using drugs during pregnancy.

Alternative medicine in irritable bowel syndrome

Because of the limited efficacy of prescribed medicines for IBS, some nonpregnant individuals turn to alternative medicines for symptomatic relief. Open trials report benefits from arrowroot and artichoke leaf. Placebo-controlled studies of probiotic therapies, such as lactobacillus and *Streptococcus faecium*, have yielded variable results ranging from efficacy to no benefit [110]. In a large placebo-controlled, double-blind trial, *Fumaria officinalis*, *Curcuma xanthorrhiza*, Ayurvedic, or spagyric remedies did not improve abdominal pain, stool function, or quality of life as compared to placebo. Contrariwise, in a randomized, controlled 16-week trial, traditional Chinese herbal medicine produced improvements in bowel symptoms and global well being, as rated by patients and their gastroenterologists [111]. An uncontrolled study noted reduced bloating and enhanced well being with acupuncture. The safety and efficacy of these alternative treatments in pregnant women with IBS are unknown.

Approach to different subsets of irritable bowel syndrome patients

The management of the pregnant patient with IBS depends on the predominant symptom. Directed therapy to treat the predominant symptom is given for a three- to six-week trial before embarking on extensive diagnostic evaluation [65].

The constipation-predominant patient

The management of the pregnant patient with IBS who has constipation involves increasing stool water and bulk. Fiber supplements are highly effective for this purpose. They should be introduced gradually to prevent abdominal gas and bloating. Drugs that slow colonic transit should be discontinued. When the response to fiber is inadequate, an osmotic laxative is recommended. Radiographic studies to assess colonic motor function should be deferred until after delivery. Laboratory studies can screen for porphyria or heavy metal toxicity if clinically suspected.

The diarrhea-predominant patient

The goal of therapy for diarrhea in IBS is to reduce stool frequency and urgency and to improve stool consistency. Kaolin and pectin can be used safely but may be inadequate for symptomatic relief. Loperamide usually is more effective, but should be used judiciously and infrequently. Bile acid-binding agents or antispasmodics reduce postprandial diarrhea, but should be employed with caution. Tricyclic antidepressants should be avoided if possible. Patients not responsive to these therapies may require additional testing. Quantitative analysis of stool volume and fat can exclude secretory diarrhea or malabsorption. Screening tests for laxative abuse are indicated for refractory or atypical symptoms.

Painful irritable bowel syndrome

Controlling the pain of IBS during pregnancy can be challenging. Narcotics should be avoided because of the risks of tolerance and dependence. As mentioned previously, antispasmodics should be used cautiously and antidepressants should not be given if possible. Investigation of the cause of pain should focus on objective historical findings, physical signs, and routine laboratory tests. Serum biochemical parameters of liver and pancreatic function should be determined if hepatobiliary or pancreatic disease is suspected. Patients occasionally need laboratory testing to exclude lead toxicity or porphyria.

Acknowledgments

Supported in part by National Institutes of Health grant 1 K24 DK02726-01.

References

- [1] Thompson WG, Longstreth G, Drossman DA, et al. Functional bowel disorders and functional abdominal pain. In: Drossman DA, Corazziari E, Talley NJ, Thompson WG, Whitehead WE, editors. *Rome II: The functional gastrointestinal disorders*. 2nd edition. McLean (VA): Degnon Associates; 2000. p 351–432.
- [2] Jackson NA, Houghton LA, Whorwell PJ, Currer B. Does the menstrual cycle affect anorectal physiology? *Dig Dis Sci* 1994;39:2607–11.
- [3] Greenhalf JO, Leonard HS. Laxative in the treatment of constipation in pregnant and breast-feeding mother. *Practitioner* 1973;210:259–63.
- [4] Levy N, Lemberg E, Sharf M. Bowel habits in pregnancy. *Digestion* 1977;4:216–22.
- [5] Heitkemper MM, Jarrett M. Pattern of gastrointestinal and somatic symptoms across the menstrual cycle. *Gastroenterology* 1992;102:505–13.
- [6] 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.
- [7] Lee OY, Mayer EA, Schmulson M, et al. Gender-related differences in IBS symptoms. *Am J Gastroenterol* 2001;96:2184–93.
- [8] Moore J, Barlow D, Jewell D, Kennedy S. Do gastrointestinal symptoms vary with the menstrual cycle? *Br J Obstet Gynaecol* 1998;105:1322–5.
- [9] Rogers J, Henry MM, Misiewicz JJ. Increased segmental activity and intraluminal pressures in the sigmoid colon of patients with the irritable bowel syndrome. *Gut* 1989;30:634–41.
- [10] Whitehead WE, Engel BT, Schuster MM. Irritable bowel syndrome: physiological and psychological differences between diarrhea-predominant and constipation-predominant patients. *Dig Dis Sci* 1980;25:404–13.
- [11] Lembo T, Naliboff BD, Matin K, et al. Irritable bowel syndrome patients show altered sensitivity to exogenous opioids. *Pain* 2000;87:137–47.
- [12] Chan YK, Herkes GK, Badcock C, et al. Alterations in cerebral potentials evoked by rectal distension in irritable bowel syndrome. *Am J Gastroenterol* 2001;96:2413–7.
- [13] Mertz H, Morgan V, Tanner G, et al. Regional cerebral activation in irritable bowel syndrome and control subjects with painful and nonpainful rectal distention. *Gastroenterology* 2000;118:842–8.
- [14] Creed F, Guthrie E. Psychological factors in the irritable bowel syndrome. *Gut* 1987;28:1307–18.
- [15] Drossman DA, Leserman J, Nachman G, et al. Sexual and physical abuse in women with functional or organic gastrointestinal disorders. *Ann Intern Med* 1990;113:828–33.
- [16] Pimentel M, Chow EJ, Lin HC. Eradication of small intestinal bacterial overgrowth reduces symptoms of irritable bowel syndrome. *Am J Gastroenterol* 2000;95:3503–6.
- [17] Niec AM, Frankum B, Talley NJ. Are adverse food reactions linked to irritable bowel syndrome? *Am J Gastroenterol* 1998;93:2184–90.
- [18] Bearcroft CP, Perrett D, Farthing MJ. Postprandial plasma 5-hydroxytryptamine in diarrhoea predominant irritable bowel syndrome: a pilot study. *Gut* 1998;42:42–6.
- [19] Morris-Yates A, Talley NJ, Boyce PM, et al. Evidence of a genetic contribution to functional bowel disorder. *Am J Gastroenterol* 1998;93:1311–7.
- [20] Battaglia G, Morselli-Labate AM, Camarri E, et al. Otilonium bromide in irritable bowel syndrome: a double-blind, placebo-controlled, 15-week study. *Aliment Pharmacol Ther* 1998;12:1003–10.
- [21] Hertzberg T, Wahlbeck K. The impact of pregnancy and puerperium on panic disorder: a review. *J Psychosom Obstet Gynecol* 1999;20:59–64.
- [22] Campbell EA. Neurotic disturbance in pregnancy—a review. *Psychiatr Dev* 1988;6:311–28.
- [23] Hendrick V, Altshuler L, Cohen L, Stowe Z. Evaluation of mental health and depression during pregnancy: position paper. *Psychopharmacol Bull* 1998;34:297–9.

- [24] Altschuler LL, Hendrick V, Cohen LS. Course of mood and anxiety disorders during pregnancy and the postpartum period. *J Clin Psychiatr* 1998;59(Suppl 2):29–33.
- [25] Fava GA, Grandi S, Michelacci L, et al. Hypochondriacal fears and beliefs in pregnancy. *Acta Psychiatr Scand* 1990;82:70–2.
- [26] Savron G, Grandi S, Michelacci L, et al. Hypochondriacal symptoms in pregnancy. *Psychother Psychosom* 1989;52:106–9.
- [27] Lips HM. A longitudinal study of the reporting of emotional and somatic symptoms during and after pregnancy. *Soc Sci Med* 1985;21:631–40.
- [28] Hinds JP, Stomey B, Wald A. Does gender or the menstrual cycle affect colonic transit? *Am J Gastroenterol* 1989;84:123–6.
- [29] Kamm MA, Farthing MJ, Lennard-Jones JE. Bowel function and transit during the menstrual cycle. *Gut* 1989;30:605–8.
- [30] Turnbull GK, Thompson DG, Day S, et al. Relationships between symptoms, menstrual cycle and oro-caecal transit in normal and constipated women. *Gut* 1989;30:30–4.
- [31] Wald A, Van Thiel DH, Hoehstetter L, et al. Gastrointestinal transit: the effect of the menstrual cycle. *Gastroenterology* 1981;80:1497–500.
- [32] Aytug N, Giral A, Imeryuz N, et al. Gender influence on jejunal migrating motor complex. *Am J Physiol* 2001;280:G255–63.
- [33] Cabellero-Plasencia AM, Valenzuela-Barranco M, Martin-Ruiz JL, et al. Are there changes in gastric emptying during the menstrual cycle? *Scand J Gastroenterol* 1999;34:772–6.
- [34] Knight LC, Parkman HP, Brown KL, et al. Delayed gastric emptying and decreased antral contractility in normal premenopausal women compared with men. *Am J Gastroenterol* 1997;92:968–75.
- [35] Parkman HP, Harris AD, Miller MA, Fisher R. Influence of age, gender, and menstrual cycle on the normal electrogastrogram. *Am J Gastroenterol* 1996;91:127–33.
- [36] Gill RC, Murphy PD, Hooper HR, et al. Effect of the menstrual cycle on gastric emptying. *Digestion* 1987;36:168–74.
- [37] Mones J, Carrio I, Calabuig R, et al. Influence of the menstrual cycle and of menopause on the gastric emptying rate of solids in female volunteers. *Eur J Nuc Med* 1993;20:600–2.
- [38] Bajaj P, Arendt-Neilsen L, Bajaj P, Madsen H. Sensory changes during the ovulatory phase of the menstrual cycle in healthy women. *Eur J Pain* 2001;5:135–44.
- [39] Mayer EA, Naliboff B, Lee O, et al. Review article: gender-related differences in functional gastrointestinal disorders. *Aliment Pharmacol Ther* 1999;13(Suppl 2):65–9.
- [40] Houghton LA, Jackson NA, Whorwell PJ, Morris J. Do male sex hormones protect from irritable bowel syndrome? *Am J Gastroenterol* 2000;95:2296–300.
- [41] Kamm MA, Farthing MJ, Lennard-Jones JE, et al. Steroid hormone abnormalities in women with severe idiopathic constipation. *Gut* 1991;32:80–4.
- [42] Chiloiro M, Darconza G, Piccioli E, et al. Gastric emptying and oro-cecal transit time in pregnancy. *J Gastroenterol* 2001;36:538–43.
- [43] Wald A, Van Thiel DH, Hoehstetter L, et al. Effect of pregnancy on gastrointestinal transit. *Dig Dis Sci* 1982;27:1015–8.
- [44] Ryan JP. Effect of pregnancy on intestinal transit: comparison of results using radioactive and non-radioactive test meals. *Life Sci* 1982;31:2635–40.
- [45] Scott LD, Lester R, Van Thiel DH, Wald A. Pregnancy-related changes in small intestinal myoelectric activity in the rat. *Gastroenterology* 1983;84:301–5.
- [46] Levy DM, William OA, Magides AD, Reilly CS. Gastric emptying is delayed at 8–12 weeks' gestation. *Br J Anaesth* 1994;73:237–8.
- [47] Macfie AG, Magides AD, Richmond MN, Reilly CS. Gastric emptying in pregnancy. *Br J Anaesth* 1991;67:54–7.
- [48] Whitehead EM, Smith M, Dean Y, O'Sullivan G. An evaluation of gastric emptying times in pregnancy and the puerperium. *Anaesthesia* 1993;48:53–7.
- [49] Ryan JP, Bhojwani A, Wang MB. Effect of pregnancy on gastric motility in vivo and in vitro in the guinea pig. *Gastroenterology* 1987;93:29–34.

- [50] Shah S, Hobbs A, Singh R, et al. Gastrointestinal motility during pregnancy: role of nitrergic component of NANC nerves. *Am J Physiol* 2000;279:R1478–85.
- [51] Mathias JR, Clench MH. Relationship of reproductive hormones and neuromuscular disease of the gastrointestinal tract. *Dig Dis* 1998;16:3–13.
- [52] Gill RC, Bowes KL, Kingma YJ. Effect of progesterone on canine colonic smooth muscle. *Gastroenterology* 1985;88:1941–7.
- [53] Oh ST, Yedidag E, Bielefeldt K. Differential effects of progesterone and its analogues on the contractility of the murine jejunum in vitro. *J Surg Res* 1998;75:1–15.
- [54] Chen TS, Doong ML, Chang FY, et al. Effects of sex steroid hormones on gastric emptying and gastrointestinal transit in rats. *Am J Physiol* 1995;268:G171–6.
- [55] Coskun T, Sevinc A, Tevetoglu I, et al. Delayed gastric emptying in conscious male rats following chronic estrogen and progesterone treatment. *Res Exp Med* 1995;195:49–54.
- [56] Walsh JW, Hasler WL, Nugent CE, Owyang C. Progesterone and estrogen are potential mediators of gastric slow-wave dysrhythmias in nausea of pregnancy. *Am J Physiol* 1996; 270:G506–14.
- [57] Ryan JP, Bhojwani A. Colonic transit in rats: effect of ovariectomy, sex steroid hormones, and pregnancy. *Am J Physiol* 1986;251:G46–50.
- [58] Dawson-Basoa ME, Gintzler AR. Estrogen and progesterone activate spinal kappa-opiate receptor analgesic mechanisms. *Pain* 1996;64:608–15.
- [59] Ducker TE, Boss JW, Altug SA, et al. Luteinizing hormone and human chorionic gonadotropin fragment the migrating motor complex in rat small intestine. *Neurogastroenterol Motil* 1996;8:95–100.
- [60] Bani D, Baccari MC, Quattrone S, et al. Relaxin depresses small bowel motility through a nitric oxide-mediated mechanism. *Studies in mice. Biol Reprod* 2002;66:778–84.
- [61] Manning AP, Thompson WG, Heaton KW, Morris AF. Towards positive diagnosis of the irritable bowel. *BMJ* 1978;2:653–4.
- [62] Kruis W, Thieme C, Weinzierl M, et al. A diagnostic score for the irritable bowel syndrome: its value in the exclusion of organic disease. *Gastroenterology* 1984;87:1–7.
- [63] Vanner SJ, Depew WT, Paterson WG, et al. Predictive value of the Rome criteria for diagnosing the irritable bowel syndrome. *Am J Gastroenterol* 1999;94:2912–7.
- [64] Drossman DA, Whitehead WE, Camilleri M. American Gastroenterological Association medical position statement: irritable bowel syndrome. *Gastroenterology* 1997;112:2118–9.
- [65] Sanders DS, Carter MJ, Hurlstone DP, et al. Association of adult coeliac disease with irritable bowel syndrome: a case control study in patients fulfilling Rome II criteria referred to secondary care. *Lancet* 2001;358:1504–8.
- [66] Hamm LR, Sorrells SC, Harding JP, et al. Additional investigations fail to alter the diagnosis of irritable bowel syndrome in subjects fulfilling the Rome criteria. *Am J Gastroenterol* 1999;94:1279–82.
- [67] Cappell MS, Sidhom O, Colon V. A study at ten medical centers of the safety and efficacy of 48 flexible sigmoidoscopies and 8 colonoscopies during pregnancy with follow-up of fetal outcome and with comparison to control groups. *Dig Dis Sci* 1996; 41:2353–60.
- [68] Muller-Lissner SA. Effect of wheat bran on weight of stool and gastrointestinal transit time: a meta analysis. *BMJ* 1988;296:615–7.
- [69] Hotz J, Plein K. Effectiveness of plantago seed husks in comparison with wheat bran on stool frequency and manifestations of irritable colon syndrome with constipation. *Med Klin* 1994;89:645–51.
- [70] Anderson AS. Dietary factors in the aetiology and treatment of constipation during pregnancy. *Br J Obstet Gynaecol* 1986;93:245–9.
- [71] Anderson AS, Whichelow MJ. Constipation during pregnancy: dietary fibre intake and the effect of fibre supplementation. *Human Nutr Appl Nutr* 1985;39:202–7.
- [72] Muller M, Jaquenoud E. Treatment of constipation in pregnant women. A multicenter study in a gynaecological practice. *J Suisse Med* 1995;125:1689–93.

- [73] Lewis JH, Weingold AB. The use of gastrointestinal drugs during pregnancy and lactation. *Am J Gastroenterol* 1985;80:912–23.
- [74] Nelson MM, Forfar JO. Association between drugs administered during pregnancy and congenital abnormalities of the fetus. *BMJ* 1971;1:523–7.
- [75] West L, Warren J, Cutts T. Diagnosis and management of irritable bowel syndrome, constipation, and diarrhea in pregnancy. *Gastroenterol Clin North Am* 1992;21:793–802.
- [76] Einarson A, Mastroiacovo P, Arnon J, et al. Prospective, controlled, multicentre study of loperamide in pregnancy. *Can J Gastroenterol* 2000;14:185–7.
- [77] Siebert JR, Barr M, Jackson JC, et al. Ebstein's anomaly and extracardiac defects. *Am J Dis Child* 1989;143:570–2.
- [78] Laatikainen T. Effect of cholestyramine and phenobarbital on pruritus and serum bile acid levels in cholestasis of pregnancy. *Am J Obstet Gynecol* 1978;132:501–6.
- [79] Patterson EC, Staszak DJ. Effects of geophagia (kaolin ingestion) on the maternal blood and embryonic development in the pregnant rat. *J Nutr* 1997;107:2020–5.
- [80] Poynard T, Naveau S, Mory B, Chaput JC. Meta-analysis of smooth muscle relaxants in the treatment of irritable bowel syndrome. *Aliment Pharmacol Ther* 1994;8:499–510.
- [81] Poynard T, Regimbeau C, Benhamou Y. Meta-analysis of smooth muscle relaxants in the treatment of irritable bowel syndrome. *Aliment Pharmacol Ther* 2001;15:355–61.
- [82] Pittler MH, Ernst E. Peppermint oil for irritable bowel syndrome: a critical review and metaanalysis. *Am J Gastroenterol* 1998;93:1131–5.
- [83] Correy JF, Newman NM, Collins JA, et al. Use of prescription drugs in the first trimester and congenital malformations. *Aust N Z J Obstet Gynaecol* 1991;31:340–4.
- [84] Gibson GT, Colley DP, McMichael AJ, Hartshorne JM. Congenital anomalies in relation to the use of doxylamine/dicyclomine and other antenatal factors: an ongoing prospective study. *Med J Aust* 1981;1:410–4.
- [85] McCredie J, Kricker A, Elliott J, et al. The innocent bystander: doxylamine/dicyclomine/pyridoxine and congenital limb defects. *Med J Aust* 1984;140:525–7.
- [86] Rothman KJ, Flyler DC, Goldblatt A, et al. Exogenous hormones and other drug exposures of children with congenital heart disease. *Am J Epidemiol* 1979;109:433–9.
- [87] Shapiro S, Heinonen OP, Siskind V, et al. Antenatal exposure to doxylamine succinate and dicyclomine hydrochloride (Bendectin) in relation to congenital malformations, perinatal mortality rate, birth weight, and intelligence quotient score. *Am J Obstet Gynecol* 1977;128:480–5.
- [88] Sjoqvist F, Bergfors PG, Borga O, et al. Plasma disappearance of nortriptyline in a newborn infant following placental transfer from an intoxicated mother: evidence of drug metabolism. *J Pediatr* 1972;80:496.
- [89] Tack JF, Vos R, Broekaert D, et al. Influence of citalopram, a selective serotonin reuptake inhibitor, on colonic tone and sensitivity in man [abstract]. *Gastroenterology* 2000; 118:998.
- [90] Broekaert D, Vos R, Gevers AM, et al. A double-blind randomised placebo-controlled crossover trial of citalopram, a selective 5-hydroxytryptamine reuptake inhibitor, in irritable bowel syndrome [abstract]. *Gastroenterology* 2001;120:3250.
- [91] Jackson JL, O'Malley PG, Tomkins G, et al. Treatment of functional gastrointestinal disorders with antidepressant medications: a meta-analysis. *Am J Med* 2000;108:65–72.
- [92] Clouse RE, Prakash C, Anderson RJ, Lustman PJ. Antidepressants for functional gastrointestinal symptoms and syndromes: a meta-analysis [abstract]. *Gastroenterology* 2001;120:3252.
- [93] Eggermont E, Raveschot J, Deneve V, et al. The adverse influence of imipramine on the adaptation of the newborn infant to extrauterine life. *Acta Paediatr Belg* 1972;26:197–204.
- [94] Misri S, Sivertz K. Tricyclic drugs in pregnancy and lactation: a preliminary report. *Int J Psychiatry Med* 1991;21:157–71.
- [95] Addis A, Koren G. Safety of fluoxetine during the first trimester of pregnancy: a meta-analytical review of epidemiological studies. *Psychol Med* 2000;30:89–94.

- [96] Pastuszak A, Schick-Boschetto B, Zuber C, et al. Pregnancy outcome following first-trimester exposure to fluoxetine (Prozac). *JAMA* 1993;269:2246–8.
- [97] Kulin NA, Pastuszak A, Sage SR, et al. Pregnancy outcome following maternal use of the new selective serotonin reuptake inhibitors: a prospective controlled multicenter study. *JAMA* 1998;279:609–10.
- [98] Nordeng H, Lindemann R, Perminov KV, Reikvam A. Neonatal withdrawal syndrome after in utero exposure to selective serotonin reuptake inhibitors. *Acta Paediatr* 2001;90:288–91.
- [99] Nulman I, Rovet J, Stewart DE, et al. Neurodevelopment of children exposed in utero to antidepressant drugs. *N Engl J Med* 1997;336:258–62.
- [100] Hostetter A, Stowe ZN, Strader JR, et al. Dose of selective serotonin uptake inhibitors across pregnancy: clinical implications. *Depress Anxiety* 2000;11:51–7.
- [101] Wisner KL, Perel JM, Wheeler SB. Tricyclic dose requirements across pregnancy. *Am J Psychiatry* 1993;150:1541–2.
- [102] Suarez F, Levitt MD, Adshear J, Barkin JS. Pancreatic supplements reduce symptomatic response of healthy subjects to a high fat meal. *Dig Dis Sci* 1999;44:1317–21.
- [103] Wilson J. Use of sodium cromoglycate during pregnancy: results on 296 asthmatic women. *Acta Therapeutica* 1982;8:45–51.
- [104] Dolovitch LR, Addis A, Regis JM, et al. Benzodiazepine use in pregnancy and major malformations or oral cleft: meta-analysis of cohort and case-control studies. *BMJ* 1998;317:839–43.
- [105] Weber LW. Benzodiazepines in pregnancy—academic debate or teratogenic risk? *Biol Res Pregnancy Perinatol* 1985;6:151–67.
- [106] Talley NJ, Owen BK, Boyce P, Paterson K. Psychological treatments for irritable bowel syndrome: a critique of controlled treatment trials. *Am J Gastroenterol* 1996;91:277–83.
- [107] Heymann-Monnikes I, Arnold R, Florin I, et al. The combination of medical treatment plus multicomponent behavioral therapy is superior to medical treatment alone in the therapy of irritable bowel syndrome. *Am J Gastroenterol* 2000;95:981–94.
- [108] Houghton LA, Heyman DJ, Whorwell PJ. Symptomatology, quality of life and economic features of irritable bowel syndrome—the effect of hypnotherapy. *Aliment Pharmacol Ther* 1996;10:91–5.
- [109] Nobaek S, Johansson ML, Molin G, et al. Alteration of intestinal microflora is associated with reduction in abdominal bloating and pain in patients with irritable bowel syndrome. *Am J Gastroenterol* 2000;95:1231–8.
- [110] Bensoussan A, Talley NJ, Hing M, et al. Treatment of irritable bowel syndrome with Chinese herbal medicine: a randomized controlled trial. *JAMA* 1998;280:1585–9.
- [111] Hahn B, Watson M, Yan S, et al. Irritable bowel syndrome symptom patterns: frequency, duration, and severity. *Dig Dis Sci* 1998;43:2715–8.