IRRITABLE BOWEL SYNDROME AND ENDOMETRIOSIS: IS THERE A CONNECTION?

A thesis submitted to the University of Manchester for the Degree of Doctor of Philosophy (PhD) in the Faculty of Medical and Human Sciences

2012

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The School of Translational Medicine
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ABSTRACT

Candidate name: Basma Issa
Degree title: Degree of Doctor of Philosophy (PhD) in the Faculty of Medical and Human Sciences at The University of Manchester 2012
Thesis title: Irritable bowel syndrome and endometriosis: is there a connection?
Background: Irritable bowel syndrome (IBS) is an extremely common condition affecting approximately 10-15% of the population. Lower abdominal pain is a common feature and, if the patient also has gynaecological symptoms such as heavy periods, they may be referred to a gynaecologist especially when the bowel symptoms are relatively mild. In this setting a laparoscopy is often undertaken and endometriosis commonly identified as this condition affects up to 10% of women. Consequently pain is frequently attributed to the endometriosis even when it is relatively mild. However it is a common observation amongst gynaecologists that women with mild endometriosis often have severe symptoms which do not seem to respond well to treatment. This raises the possibility that their pain may not actually be due to endometriosis or is being amplified by the visceral hypersensitivity which is a characteristic feature of irritable bowel syndrome.

Methods: 20 patients with minimal-mild endometriosis, 20 with moderate-severe endometriosis, 20 healthy volunteers (HV) who have had laparoscopy for sterilisation, 20 IBS patients and 20 patients with pain who were found to have a normal pelvis (on laparoscopy) were studied. Gastrointestinal, gynaecological, and noncolonic symptoms were recorded as well as demography, quality of life and psychological status. Visceral sensitivity was assessed in all patients and abdominal distension was studied in a sub group of 26 endometriosis patients and 20 IBS patients.

Results: 20 (100%) of IBS patients, 13 (65%) of minimal-mild endometriosis patients, 11 (55%) of moderate-severe endometriosis patients, 17 (85%) of laparoscopic negative pain patients and no healthy volunteers fulfilled ROME III criteria for IBS. Patients with endometriosis and IBS had similar levels of visceral sensitivity which were significantly lower than that observed in controls (p=0.002, p<0.001). In particular, both minimal-mild and moderate-severe endometriosis patients had significantly lower (mean-95% CI) pain thresholds in mmHg 28.1(24.5, 31.6) and 28.8(24.9, 32.6) respectively compared with controls 39.5 (36.0, 43.0) p=0.001 and p=0.002. However, with few exceptions, there were no distinguishing features between patients in terms of demography, symptomatology and distension.

Conclusion: Clinically, it is very difficult to distinguish between endometriosis and IBS. However, visceral hypersensitivity appears to be a major component of endometriosis and may explain the problem of excessive pain especially in patients with mild disease offering a potential new target for treatment.
DECLARATION

**Name of the University:** The University of Manchester

**Candidate name:** Basma Issa

**Degree title:** Degree of Doctor of Philosophy (PhD)

**Faculty:** Faculty of Medical and Human Sciences

**Thesis title:** The importance of visceral hypersensitivity in patients with endometriosis

**Date:** 2012

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This thesis would not have been possible without the enormous support I had from my husband Najem. I should not also forget my children Nizar, Ameir and Tameem who have also been very understanding.

To my Mum and Dad, I’m so proud of you and so lucky to have you. Thank you for everything you’ve done for me throughout my life. As a small token of gratefulness, appreciation and love, I would like to dedicate this thesis to you both.
PREFACE

After graduating from the medical school in 1993 and specialising in radiology, I worked for few years in the department of radiology at the women’s hospital back home. After moving to the UK, I completed an MPhil degree at Manchester University in 2005 in the field of imaging sciences before joining Professor Whorwell’s research team at South Manchester University Hospital in 2007.

During my practice in radiology, I have dealt with a wide range of female patients who were referred for investigation of pelvic pain. Therefore, this particular project, looking at IBS and endometriosis, was of great interest to me.
BACKGROUND

Irritable bowel syndrome (IBS) is an extremely common condition affecting approximately 10-15% of the population. It is characterised by a combination of abdominal pain, abdominal bloating or distension and an abnormal bowel habit which can take the form of diarrhoea, constipation or an alternation between the two. In addition, these patients frequently suffer a variety of non-colonic symptoms such as low backache, lethargy, nausea and bladder symptoms which can take the form of frequency or urgency of passing urine. Females with IBS also suffer from gynaecological symptoms such as painful periods and a particular problem is pain on intercourse which can seriously interfere with their sex life (1, 2).

When the symptoms of a patient with IBS are predominantly gastrointestinal in origin then the usual referral route to secondary care is to a gastroenterologist. However, if the non-colonic symptoms are particularly troublesome then the referral pattern can be rather different. For instance, if bladder symptoms are prominent then the patient might be referred to a urologist (3) and if back pain is an issue it is possible that an orthopaedic referral might be made (4). In women with IBS who also have gynaecological symptoms then, if these are particularly
prominent, or the bowel symptoms are relatively mild, a gynaecological referral might be considered appropriate. Consequently, IBS patients might be referred to gynaecological clinics because of their IBS related non-colonic symptoms rather than the fact that they actually have gynaecological pathology. This possibility has been investigated in the past and it has been shown that up to 50% of women attending gynaecological clinics with abdominal pain do actually appear to have irritable bowel syndrome (5). Not surprisingly, these patients have a rather poor outcome as they do not have any gynaecological pathology.

Endometriosis is also an extremely common disorder with a prevalence not that much different to IBS in the order of 7-10% of women worldwide rising to 30%-50% in patients with infertility, pain or both (6-10). This condition is also characterised by abdominal pain and often the level of pain seems to be out of proportion to the severity of the endometriosis when it is seen at laparoscopy. Quite often patients with minimal endometriosis appear to have particularly severe pain and even when the condition is treated the pain may not necessarily settle down. This raises the possibility that there may be an alternative explanation for the severity of their symptoms. One possibility is that their minimal endometriosis is not causing a great deal of pain and that their pain is actually coming from IBS, especially as IBS patients are known to be commonly referred to gynaecological clinics. Another explanation is that the visceral hypersensitivity that is characteristic of IBS may be playing a part. It has been known for many years that patients with IBS exhibit increased sensitivity to balloon distension of the rectum and this is called visceral
hypersensitivity (11, 12). It has also been shown that this visceral hypersensitivity is not necessarily confined to the rectum (11, 13). This raises the possibility that if visceral hypersensitivity is more widespread and possibly affecting the peritoneal cavity, it might be amplifying the pain of otherwise mild endometriosis.

These observations raise the possibility that being alert to a potential overlap between irritable bowel syndrome and endometriosis might lead to more effective management strategies especially for patients with relatively mild endometriosis in whom symptoms seem to be out of proportion to the clinical findings. It was therefore, the purpose of this thesis to investigate the possibility that irritable bowel syndrome and/or visceral hypersensitivity might be confusing the diagnosis of abdominal pain in women.

In order to investigate this possibility an in depth assessment of symptoms of both a gastrointestinal and gynaecological nature was undertaken in patients with endometriosis and various comparator groups in conjunction with the measurement of visceral sensation in these patients using a barostat. It was also felt that an assessment of bloating and distension would be a useful additional line of enquiry. Bloating, where a patient feels a sensation of increased pressure in their abdomen, and distension where this sensation is accompanied by an actual increase in girth, are both common features of IBS and the latter can now be assessed objectively by a technique called abdominal inductance plethysmography. Consequently, there follow chapters describing visceral
hypersensitivity, bloating, distension, abdominal symptoms, quality of life, non-colonic symptoms, mood and demography in patients with endometriosis, irritable bowel syndrome, laparoscopic negative abdominal pain and healthy volunteers who had had a laparoscopy for the purpose of sterilisation.
CHAPTER ONE: INTRODUCTION
1.1 IRRITABLE BOWEL SYNDROME (IBS)

Irritable bowel syndrome (IBS) is a functional gastrointestinal disorder characterised by abdominal pain or discomfort that is usually relieved by defecation. An altered bowel habit is another feature and most sufferers also complain of abdominal bloating or distension. IBS affects between 10%-15% of the general population, is more dominant in female patients (14, 15) and can have a negative impact on patients’ quality of life (16).

1.1.1 Pathophysiology

Different pathogenic theories related to IBS have been suggested. Some of these are linked to motility (17, 18), inflammation (19, 20), a disturbance in brain-gut interaction (8, 21, 22), visceral sensitivity (8), hormones (23), genetic (24), or response to environmental events (25). Psychological effects may also play a role in IBS (26) such as a history of child abuse (27), traumatic life events, panic, anxiety, stress, or mood disorders (28).

1.1.1.1 Altered motility

Researchers have examined the theory that altered GI motility is involved in IBS by looking at the differences between IBS patients and healthy controls.
Unfortunately, there appear to be no consistent corresponding patterns of disordered motility that are responsible for diarrhoea or constipation. However, diarrhoea is usually associated with short time transit while delayed transit is noted in constipation (26).

1.1.1.2 Visceral Sensitivity

Visceral sensitivity was first mentioned in 1973 by Ritchie who found that IBS patients had a lower threshold for visceral pain than controls when a balloon was inflated in the rectum (11). Other studies later reported similar findings (29). A possible consequence of this might be that IBS patients are more likely than controls to notice intestinal contractions and gas (18). What is more, hypersensitivity has been noted throughout the GI tract and a positive correlation was noted between patients’ pain threshold and their clinical pain (26).

It has been suggested that visceral sensitivity might be a biological marker of IBS (30, 31), giving the potential for differentiating the symptoms of this disorder from other conditions (32). This is a very interesting finding, however, some researchers have suggested that hypersensitivity might be due to the extra attention to bodily sensation and central sensitisation which may be the reason behind increasing pain (33).

In a study done by Andresen that was published in 2009, visceral hypersensitivity was considered a vital factor in the pathogenesis of functional gastrointestinal disorders (34). Andresen mentioned that assessing visceral sensitivity is a very
important step to a better understanding of the normal and abnormal visceral sensory mechanisms. He also believed that such assessment could help in identifying patients with abnormal visceral sensitivity and may have an important implication on the management and therapy designed for these patients.

Barostat or what is called the rectal distension test, is frequently used in visceral sensitivity tests (35). A threshold is usually measured for urgency, discomfort, or pain and the ascending methods of limits is frequently performed as well as random sequence to minimise variation in response (35).

It has been suggested that visceral hypersensitivity may cause abdominal discomfort or pain. Previous studies have shown that altered gut microflora might lead to visceral hypersensitivity. Verdu and colleagues looked at the effect of probiotics on reducing visceral sensitivity in mice by changing the gut microflora (36). They found that mice who had received antibiotic treatment developed both changes in the gut microflora and hypersensitivity. However, normal visceral sensitivity was achieved when a probiotic (Lactobacillus) was administered. This showed that changes in gut flora play an important role in functional gastrointestinal disorders; and that probiotics prevented antibiotic-induced visceral hypersensitivity in mice (36).

Another study on a rat model (37), involved measuring visceral sensitivity in rats. Rats were subjected to partial restraint stress by separating new born rats from their mothers for 3 days. Hypersensitivity (demonstrated by increased cramp like
contractions during rectal distension) was assessed after fifteen days of oral administration of Bifidobacterium animalis subsp. lactis DN-173 010 or placebo. This study showed that probiotic treatment resulted in a significant reduction of the number of cramps during the rectal distension compared with controls who received (Man-Rogosa-Sharp) MRS growth medium (37).

Over the last two decades extensive clinical research has been done in this area. Abnormal responses in patients with irritable bowel syndrome (IBS) were reported and more research is always beneficial to add to our understanding in this field, however, to date, no study has investigated the relationship between visceral hypersensitivity and endometriosis.

1.1.1.3 Central Nervous System Modulation

The pathophysiological mechanisms responsible for this disorder are also still not very clear. Brain- gut interactions are believed to play a major role in gut function in both patients and healthy candidates.

Some research suggests that the extrinsic nervous system of sympathetic and parasympathetic supply to the gut (the spinal cord, brain and cortex), modulates the gut function (38). The extrinsic nervous system which includes transmitters released from the enteric neurons such as acetylcholine (ACh) for example, also play a role in the pathophysiology of gastrointestinal functional disorders. Therefore, any changes in brain gut coalition may lead to GI dysfunction (33).
In IBS, normal physiological gut and visceral stimulus are perceived in a negative way. In other words, non-painful events might be perceived as painful sensations as lower abdominal pain (39). Functional Magnetic Resonance Imaging (fMRI) has been used in several studies to understand the complex perception of visceral pain. A recent study that used fMRI stated that IBS patients may have an altered brain response to bowel stimulation (40). A number of subcortical and cortical regions might also be involved in functional pain processing (41).

In 2001, Hamdy et al. looked at patterns of responses of the oesophageal sensorimotor cortex to painful and non-painful visceral stimulation. They found that these two types of stimuli induce different patterns of oesophageal corticobulbar reaction. He found that there is a physiological link between visceral pain and the way the cortex alters function in response to a physiological input or what is called the cortical plasticity (42).

A relationship between visceral pain and cortical plasticity has also been reported in another study that looked at human oesophageal sensory-motor cortex (42). This may play an important role in future therapeutic interventions of functional visceral pain (42) as, if cortical plasticity has a role in visceral pain, blocking such activity may help to improve patients’ symptoms. Other studies have also looked at the cortical involvement in digestive sensations and further brain neuro-imaging is being considered to understand both the sensitivity and behaviour of the gastrointestinal system (43). A study which used imaging techniques in IBS
patients and controls, illustrated that the cortical activations induced by rectal
distension were different in these two groups. However, more studies are required
to support these results and to explain the roles of the peripheral and central
mechanisms of visceral hypersensitivity even more clearly (44).

1.1.1.4 Inheritance

There is no doubt that irritable bowel syndrome runs in families with a familial
prevalence as high as 40% being reported (45). However, although twin studies
suggest a genetic component, this would not account for the high prevalence of up
to 40% (46). This raises the possibility that there may be a learned component to
IBS as a consequence of offspring observing the suffering in a parent with this
condition (47). To date, there have been relatively few genetic studies in IBS and,
in those that have been done, no firm associations have yet been described (46).

1.1.1.5 Inflammation

There is some evidence that inflammation can alter the gut immune function which
may lead to IBS. Bacterial infection such as Salmonella, Shigella, E. Coli and
Campylobacter or viral infection, for example; can cause gastroenteritis. It is
thought that such infections can lead to what is called postinfectious IBS (PI-IBS)
(48). Females, smokers, vegetarians, young people and those with more than 3
weeks of inflammation have been found to have more chance of developing PI-IBS
(49). The pathophysiological mechanism for PI-IBS is not entirely clear but it is
believed that increased intestinal permeability, altered motility, chronic intestinal
inflammation and alteration of gut flora all play important roles in PI-IBS (48). A research study which focused on bacterial gastroenteritis and IBS revealed that about 7%–30% of patients who recovered from a proven bacterial gastroenteritis had IBS like symptoms (50). Recently, the pathogenic role of the intestinal microflora has been looked at and studied extensively and it will take more research work to establish a clearer view.

1.1.1.6 Bacterial imbalance and IBS

It has been suggested that there are more than 100 billion bacteria in the intestine of a human body. Microflora in the gut can be either in the lumen or associated with the mucosa. The roles they play differ accordingly (49).

Intestinal microflora helps in digesting Lactose, altering gas production in the lumen, decreasing transit time and enhancing the absorption of some minerals such as calcium, magnesium and iron. Therefore, changes in the gut flora might lead to symptoms or functional disorders. The use of antibiotics or immunosuppressive agents alters the gut microflora in addition to either surgery or gastroenteritis (51). Researchers such as Madden, Spiller and Gwee suggested that such changes to microflora might lead to IBS (51-53). A study in 1982 used microbiological techniques to examine the gut microflora in IBS patients. It demonstrated that although the quality of faecal microflora was similar in IBS and controls, there were differences in their quantity. IBS patients had less lactobacilli and bifidobacteria (54). This suggests that probiotics might have beneficial effects
in IBS, as treatment with Bifidobacterium infantis was shown to improve IBS symptoms and normalise the anti- and pro-inflammatory cytokines ratio (55).

It is now known that abnormalities of the gut microflora are found in IBS patients (56-58) and several observations suggested a role for the gut flora in IBS manifestation (36). It has been reported that patients who have received antibiotic treatment for conditions other than gastrointestinal, have a three times greater chance of developing a functional gastrointestinal disorder such as IBS (59). It is believed that factors resulting from infection and antibiotic treatment play different roles in the pathophysiology of developing IBS. These factors include changes in the gut mucosa, inflammation and changes in the immune system (20, 60).

**Small intestinal bacterial overgrowth (SIBO)**

The prevalence of small intestinal bacteria overgrowth (SIBO) is not precisely known but there is a wide debate about its role in IBS. Recent research showed that there is a possible association between the two. SIBO causes changes in the bowel such as inflammation of the mucosal membrane. It may also cause some symptoms such as abdominal pain, bloating and diarrhoea (61).

Bacterial overgrowth can be identified by measuring levels of Hydrogen in breath, the Hydrogen Breath Test (HBT), and might be treatable using non-absorbable antibiotics such as Rifaximin (62).
A study done in the USA in 2000 showed that bacterial overgrowth is associated with IBS and eradication of this overgrowth improves symptoms (63).

Overgrowth of bacteria is traditionally diagnosed by culture techniques. However, the most precise diagnosis for overgrowth of bacteria relies on molecular techniques as they have greater accuracy in identifying bacterial species which are difficult to culture (64).

Another study done by Carrara and colleagues in Italy, also investigated the association between IBS and small intestinal bacterial overgrowth (SIBO) using a Lactulose Breath Test (LBT). They found that approximately 43% of IBS patients recruited for the study had a positive LBT (65). They concluded that SIBO is common among IBS patients and suggested that LBT is a useful diagnostic mean for detecting SIBO in IBS. This may lead to better diagnostic and management approaches in IBS patients (65).
Figure 1 The intestinal bacterial flora in normal gut and in SIBO

A: Demonstrates how digestible starch gets digested and absorbed in the proximal part of gut and only a little amount of poorly digestible starch passes to the distal ileum or colon where bacterial flora reside and ferment starch into gas. B: Shows that in SIBO, a high concentration of bacteria are present proximally and fermentation of all types of starch and gas production occurs (66). The figure was taken from a paper published by Lin HC in 2004.
**Hydrogen breath test**

The hydrogen breath test (HBT) is used in three main conditions, lactose intolerance, fructose malabsorption, and small intestinal bacterial overgrowth (SIBO). The hydrogen breath test is a diagnostic test for SIBO. In healthy individuals, large amounts of bacteria are usually located only in the colon. In patients with SIBO bacteria are retained in the small intestine. Hydrogen gas is produced by the intestinal bacterial due to fermentation of carbohydrates. The gas is then absorbed into the circulation of intestinal mucosa, before being transported to the lungs for elimination into the exhaled air. The hydrogen level can then be detected by a breath test (61).

When patients are suspected to have a lack of lactase enzyme, they are offered a breath test. A baseline breath test is taken before carbohydrates or lactose are administered orally. In the case of SIBO, H2 resulting from carbohydrate fermentation by bacteria situated in the proximal intestine will be eliminated through the exhaled air (61). The test is considered positive when an increase of more than 10 parts per million (PPM) in H2 concentration in exhaled air over the baseline is noted (61). In case of lactose intolerance, the individual affected does not digest and absorb the lactose in milk and the sugar given reaches the colon. The bacteria there digest it and produce hydrogen which causes an increase in the concentration of hydrogen in the breath.
1.1.1.7 Dietary factors

Most patients with IBS notice that their symptoms appear to be made worse when they eat a meal. This raises the possibility of some form of allergy or intolerance to food although there is no strong evidence that allergy plays an important part in IBS except possibly in more atopic patients. However, there is now accumulating evidence that patients with IBS tend to be intolerant of quite a wide range of foods. It has been known for some years that cereal fibre has the potential for making the symptoms of IBS worse (67) but more recently Fermentable, Oligo, Di- and Mono-saccharides and Polyols (FODMAPS) have also been shown to cause problems and these carbohydrates occur in many fruits and vegetables (68, 69). Consequently, avoidance of these various food groups can sometimes improve the symptoms of IBS.

1.1.1.8 Psychological factors

A range of psychological problems have been described in patients with IBS with abnormalities such as abnormal illness behaviour, poor coping skills and disordered cognitions about their illness all being described with anxiety probably being the most consistent finding. However, in a disorder which is as intrusive as IBS it is always difficult to work out whether any particular psychological abnormality is a cause or an effect. There is no doubt that the presence of anxiety will make the symptoms of IBS worse but it remains doubtful that psychological factors on their own are responsible for this condition.
1.1.2 Diagnosis

The diagnosis is usually made by taking a detailed medical, family and gastrointestinal history followed by clinical examination. IBS is diagnosed without any tests as it can be mainly identified by symptoms (70, 71). Some tests, however, like sigmoidoscopy, colonoscopy, stool examinations and lactose tolerance tests may be done to exclude other diseases such as tumours, inflammatory and coeliac diseases (72).

Some research suggests that visceral sensitivity may be considered as a biological marker of IBS (30).

Alarming symptoms such as gastrointestinal bleeding, weight loss, anaemia, fever, family history of cancer or inflammatory bowel disease, weight loss or an abdominal mass should prompt further investigations (73).

1.1.3 ROME III diagnostic criteria

Different classifications have been used to categorise IBS. The Manning Criteria, ROME II and ROME III are most commonly used.

These are the most recent diagnostic criteria for irritable bowel syndrome based on symptoms (73), and can be summarised as follows:

Recurrent abdominal pain or discomfort at least 3 days per month in the last 3 months associated with two or more of the following:
1. Improvement with defecation

2. Onset associated with a change in frequency of stool.

3. Onset associated with a change in form (appearance) of stool.

Criteria must be fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis (39).

1.1.4 IBS sub-classifications

IBS can be classified into four subgroups:

1. Constipation predominant IBS (IBS-C): those patients must have more than 25% hard or lumpy stool of their bowel movements

2. Diarrhoea predominant IBS (IBS-D): Mainly diarrhoea with more than 25% loose or watery stool of their bowel movements.

3. Mixed bowel habit group IBS (IBS-M): Also called Alternating IBS (IBS-A): These patients have 25% hard or lumpy stool and 25% watery or loose stool of their bowel movements at least.

4. Unspecified IBS when patients stool consistency does not meet any of IBS C, D or M criteria (73)
1.1.5 Colonic and noncolonic symptoms in IBS

Some patients complain of other bowel symptoms such as straining, urgency, the feeling of incomplete evacuation and the passage of mucus in the stool. Blood in the stool is not uncommon particularly if patients are straining but should always be investigated to exclude other causes. Bloating is a particularly troublesome symptom which is very common in IBS and can be accompanied by a considerable increase in abdominal girth.

Noncolonic symptoms such as fibromyalgia, low back pain, thigh pain, heartburn, headache or gynaecological and urinary symptoms can also be associated with IBS (1). These can cause diagnostic confusion and in some cases surgical interventions such as appendectomy, cholecystectomy, and hysterectomy are undertaken in these patients (4).

It is not uncommon for female IBS patients to suffer from pain during menstruation (74), and dyspareunia which can cause diagnostic confusion and inappropriate referral which might delay diagnosis.

The reason behind dyspareunia in IBS patients is not fully known, but it could be due to generalised pelvic visceral hypersensitivity (75) or as referred to by pelvic hyperalgesia (76). What is more, the female internal genital organs have similar visceral innervation to the distal GI tract. The vagina, cervix, uterine and ovaries share the same splanchnic afferent innervations as the GI tract distal to the ileum,
including the rectosigmoid (76) which might explain sexual dysfunction in IBS patients.

1.1.6 Treatment

1.1.6.1 Education and explanation

Patients who receive a firm diagnosis of IBS need to obtain sufficient information about IBS so they can understand the disease, its symptoms and why they happen. A simple explanation to the patient would be that the interaction between the brain and the gut is disturbed. The bowel in IBS patients overreacts to some external or internal stimuli such as food, hormonal changes, medications and stress. This leads to stretching the bowel resulting in pain, diarrhoea, constipation, bloating and an increase in visceral sensitivity (73).

Patients need to be aware that they can benefit greatly from adopting healthy and less stressful lifestyle routines. IBS patients must also be educated that the severity of symptoms they suffer from as well as the level of involvement of psychological issues can affect the type of treatment they will receive (73).

The disorder is not a life threatening condition but may not be completely cured. Keeping a long term good relationship between the physician and the patient increases patient’s satisfaction and reduces the frequency of patient’s health care visits (77).
1.1.6.2 Lifestyle and diet

IBS patients are advised to have regular meals and to avoid rushing their food. Specific types of food such as insoluble fibre, beans, fatty food, caffeine, chocolate, sugar substitutes and alcohol can trigger pain and other symptoms in some IBS patients (73, 78). These patients usually correlate their symptoms to a specific food intake. Hence, it is always advisable that patients try to exclude one type of food at a time for at least one month to see if their symptoms will improve (79). A study that was done in 1994 looked at the effect of fibre, specifically bran on IBS symptoms. Results revealed that more than 55% of patients involved were made worse by bran and only 10% found bran beneficial (67). This suggests that although fibre is useful for constipation, the use of bran in IBS treatment should be reconsidered. The same study mentioned that citrus fruits especially oranges also had a negative impact on some patients. Only patients themselves can determine what type of food suits them and what to avoid.

Exercise is generally considered to be beneficial in terms of promoting good health although there are relatively sparse data on its effect on gastrointestinal physiology in relation to irritable bowel syndrome. However, there has been one recent study showing some improvement in symptoms, including bloating, with relatively modest amounts of exercise (80). There have been no studies to assess whether strengthening the weak abdominal musculature, that has been previously reported, might be of any value.
1.1.6.3 Drug therapy

Antispasmodics

These are divided into two subgroups, smooth muscle relaxants such as Mebeverine and anticholinergics like Hyoscine (78). These types of medications can be taken as needed and they may help some IBS patients with their abdominal pain (78).

Antidepressants

Tricyclic antidepressants and Selective Serotonin Reuptake Inhibition therapy (SSRIs) may improve patients’ symptoms and their general quality of life. They are usually given at a low dose, to patients with moderate or severe IBS symptoms (73). One downside of tricyclics is the tendency to cause constipation and therefore a laxative treatment must be considered when it is prescribed to constipation patients. This side effect however, is not known to be associated with the SSRI group (78).

Antibiotics

Wide spectrum antibiotics have been used recently as a treatment for SIBO. Rifaximin, in particular, has been of much interest with regard to the treatment of bacterial overgrowth in IBS. Some researchers demonstrated that such wide spectrum antibiotics are more effective than the conventional ones which might lead to bacterial resistance (81). Rifaximin is a non absorbable antibiotic that has intraluminal antibacterial actions. Therefore, it is expected to cause fewer side
effects (82). Many studies have also investigated the appropriate dose of Rifaximin to be used in SIBO. One particular study summarised that a seven day treatment with a dose of 1,200 mg a day is efficient in the treatment of SIBO (83). A year later another study suggested that a 10 day treatment using the above mentioned treatment can reduce IBS symptoms for up to ten weeks after completing treatment (84).

This research supports the statement that Rifaximin can be beneficial in controlling bacterial overgrowth in the small intestine (85).

**Laxatives**

Treatment of constipation may help in reducing abdominal discomfort and a small dose of laxative such as sodium picosulphate, bisacodyl, senna or polyethylene glycol can be taken on a regular basis without any fear of damaging the bowel (78).

**Antidiarrhoeals**

Agents such as Loperamide, Diphenoxylate, and Codeine phosphate may prevent or reduce diarrhoea episodes. Patients themselves need to work out the dose that they find sufficient for their symptoms and needs (78).
Serotonin receptor antagonists

This type of treatment may decrease urgency, stool frequency and pain and can be useful in diarrhoea type IBS. Some side effects including Ischemic colitis affected the treatment popularity (73).

Probiotics

Probiotics are microorganisms found alive in foods and supplements. Many studies have showed that probiotics may have valuable use in cases of inflammation, infection, neoplastic disorders and allergic conditions. They promote phagocytosis as a first line of defence by suppressing the local inflammatory response by reducing tumour necrosis factor-alpha or TNFα Secretion. They also have an anti-inflammatory effect on the intestinal mucosa, which leads to balancing the intramucosal serotonin production. This results in decreasing abdominal distension and reducing visceral hypersensitivity and abdominal pain (49), (86) and (87). Researchers demonstrated that using "Healthy bacteria" such as Bifidobacterium and Lactobacillus can improve some IBS symptoms (55). One study showed that Bifidobacterium can help in improving transit time and abdominal girth numbers and may be useful in treating distension in IBS patients (88).

Psychological treatment

IBS symptoms are made worse by associated stress, anxiety or depression. Therefore, psychological treatment may improve gastrointestinal as well as other
symptoms (89). This treatment, however, must only be offered to patients with moderate-severe symptoms and when patients have failed medical therapy (26).

**Hypnotherapy**

Researchers have found that IBS symptoms can be relieved by hypnotherapy (90). A study by Gonsalkorale and the Manchester team demonstrated in 2003 that the positive effects of hypnotherapy on IBS patients can last as long as 5 years and may lead to a decrease in the number of patients' hospital visits and consultations (91).

1.1.6.4 The potential role of neuro-modulators on visceral sensitivity

**Visceral hypersensitivity**

As discussed above, this pathphysiological abnormality is a consistent feature of IBS. Consequently, targeting this problem with pharmacological agents is a logical step in treatment.

**Antidepressants**

There is evidence that antidepressants both Selective Serotonin Reuptake inhibitors (SSRIs) and Tricyclic Antidepressants (TCA) relieve the symptoms of IBS. The mechanism by which this happens is not entirely clear but there is a possibility that it could be due to its effect on visceral sensitivity.
Selective Serotonin Reuptake inhibitors (SSRIs)

SSRIs, such as Citalopram, Escitalopram, Fluoxetine, Fluvoxamine, Paroxetine, and Sertraline, increase 5-HT neurotransmission in the brain. They are usually better tolerated than tricyclic antidepressants and less likely to cause cardiotoxicity. The main side effects of SSRIs are nausea, insomnia, headache, anxiety, rash, sweating and sexual dysfunction (92).

Tricyclic Antidepressants (TCA)

Tricyclic Antidepressants inhibit the neuronal uptake of noradrenaline and 5-HT. Some of the TCAs are: Amitriptyline, Clomipramine, Desmethylimipramine, Dosulepin, Doxepin, Imipramine, Lofepramine, and Nortriptyline. TCAs can be used for severe or resistant cases. Treatment usually starts with low doses and these will then be gradually increased to therapeutic levels. As with most medications, they also cause some adverse effects mainly due to their anticolinergic properties. Cardiotoxicity is an important one of them, especially in overdose. Therefore, they should be used in caution in patients with heart disease (92).

Monoamine oxidase inhibitors

These are considered the 3rd line of action for cases which have failed to respond to other drug management. It may take up to 4 weeks before this treatment shows any positive effects. Monoamine oxidase inhibitors (MAOIs) block the enzyme
monoamine oxidase (type A and Type B) and hence cause an increase in brain noradrenaline and 5-HT levels. The main drugs of this group are Isocarboxazid, Phenelzine, Tranylcypromine, and Moclobemide. These may cause some side effects on the central nervous and the cardiovascular systems.

**Effects of TCA and SSRIs on VS**

There have been several meta-analyses showing that antidepressants appear to be reasonably effective in the treatment of irritable bowel syndrome. Traditionally tricyclic antidepressants are the drugs of choice and are particularly useful in the diarrhoea sub-type of IBS because of their slight tendency to cause constipation. However, they can also be useful in constipation type IBS as long as an eye is kept on the bowel habit and worsening of the constipation avoided. In addition, they only need to be used at a low a dose hence side effects can often be avoided. If tricyclic antidepressants do not help the situation or if constipation is a major problem then a Selective Serotonin Reuptake Inhibitor (SSRI) is worth considering. (21), (93) There is also now some evidence that both tricyclic antidepressants and serotonin reuptake inhibitors might also have the effect of reducing visceral hypersensitivity (93-95).

**Other neuro-modulators and IBS**

**Pregabalin**

Pregabalin is a second generation antiepileptic (96). It has recently been approved in Europe and the USA to be used in neuropathic pain, epilepsy and other
neuropathic disorders (96), (97). In a study which was done in 2007, Pregabalin was shown to have effects on rectal distension in patients with IBS. A group of hypersensitive IBS patients received either Pregabalin or placebo as a control, both for three weeks (97). A barostat test was performed twice using an ascending method of limits followed by tracking technique. The first barostat test was done before treatment and the second one was after. First sensation, first desire to defecate and pain threshold were all significantly higher after treatment in the Pregabalin group compared to those in the placebo controls (97).

These interesting results indicate that Pregabalin can decrease hypersensitivity and, therefore, may be used in patients who have increased visceral sensitivity including those with IBS or with endometriosis (97).

**Ketotifen**

Ketotifen, one of the mast cell stabilisers, has been tested on visceral sensitivity in IBS patients who were viscerally hypersensitive (98). In Klooker’s study (98), IBS patients who received Ketotifen for 8 weeks showed reduced visceral sensitivity levels on barostat measurements. Their threshold for discomfort was higher compared to those who were given placebo. However, these findings only apply to viscerally hypersensitive and not normosensitive IBS patients (98).

**Summary**

As already discussed, there are a number of pharmacological agents which have the potential of modifying visceral sensitivity. Consequently, if endometriosis
patients are found to be hypersensitive, a case could be made for undertaking clinical trials of these agents to assess whether they may be of therapeutic value in this condition.
1.2 ENDOMETRIOSIS

Endometriosis is a common chronic gynaecological disorder that affects a large number of women, it affects about 7-10% of women worldwide (6-10). It is the most common cause of pelvic pain in adolescence (99). This condition is characterised by an ectopic growth of the endometrial cells (ECs), glands and stroma, outside the uterine cavity (99, 100). It was first described by the Austrian pathologist Von Rokitansky in 1860 (101).

1.2.1 Pathophysiology

The pathogenesis of endometriosis is not yet clear and various hypotheses have been put forward to describe it. Research generally supports the concept of retrograde menstruation that leads to peritoneal seeding with endometrial tissue (102) as was originally explained by Sampson in 1927 (103). However up to 90% of women have been shown to have retrograde transport, in healthy females those misplaced ECs do not implant as they are cleared from the pelvic peritoneum by the immune system (102). Consequently, it has been suggested that women with endometriosis may have a fault in their immune system which leads to failure in clearing of the ECs and hence implantation and establishing of endometriosis.
Animal studies on non menstruating female marmoset monkeys who are known to have high circulating oestrogen levels by Einspanier in 2006 showed that endometriosis can be induced experimentally. This was possible by either flushing the uterus with endometrial cells into the abdominal cavity or by invasively implanting those cells in the peritoneal cavity, over a period of 2-3 years. 72% of the monkeys treated in this study developed endometriosis. The study showed also that a greater number of the monkeys developed endometriosis when cells were implanted invasively (104).

A few other theories were described by Baldi in 2008 such as coelomic metaplasia and anatomic abnormalities. Other theories are related to genetic and environmental factors, abnormalities in the angiogenesis process, immune system and inflammatory response.
Figure 2 Common sites for endometrial lesions.

Picture was taken from the U.S. National Library of Medicine, National Institutes of Health updated by Susan Storck.
1.2.2 Aetiological theories for endometriosis

1.2.2.1 Retrograde menstruation

This is also called the transplantation and implantation theory. It suggests that endometrial tissue is distributed via fallopian tubes as a result of retrograde menstruation and enters the peritoneal cavity where cells adhere to the peritoneal wall, proliferate, and invade the surrounding tissue (102). This explains why women with long and heavy periods have a higher prevalence of endometriosis and also the higher tendency in young women with outlet obstruction to menstrual flow to develop endometriosis (105). However, it does not explain the presence of endometriosis in distant sites such as lungs, breast or skin (106).

1.2.2.2 The metaplasia theory

Undifferentiated cells in the peritoneum may be capable of becoming endometrial tissue and this was first described by Meyer in 1919 (107).

Pelvic endometriosis may be derived through a metaplastic process occurring in the peritoneal mesothelium and can also arise from the ovarian surface epithelium. It has been suggested that endometrial stroma stimulates the metaplastic process with its rich contents of growth factors and cytokines. This theory may explain the presence of the disease in the absence of menses or retrograde menstruation (6).
1.2.2.3 Anatomic abnormalities

It is believed that anatomic abnormalities may also play a role in the pathogenesis of endometriosis. Vaginal obstruction in young females, for example, causes outflow and backwash of menstrual tissue which might be implanted in the peritoneum in the pelvic area (108).

A study which was carried out by Vercellini in 2000, about the origin of deep endometriosis, found that the depth and volume of the pouch of Douglas, is reduced in patients with deep endometriotic lesions as compared to women with a healthy pelvis (109).

1.2.2.4 Vascular/lymphatic transport

In 1949 Javert indicated that metastasis of endometrial cells via lymphatic and vascular channels to distant organs may be responsible for the development of endometriosis (110) This theory explains the very rare cases of endometriosis in the thoracic cavity, bone, breast, pancreas, and other distant sites.

1.2.2.5 Angiogenesis hypothesis

It is believed that endometriosis is one of the angiogenic diseases and there is evidence of increased endometrial angiogenesis in women with endometriosis compared to healthy volunteers. The hypothesis here is that in endometriosis patients the endometrium has an increased capacity to proliferate, implant and grow in the peritoneal cavity (111)
1.2.2.6 Direct implantation

This theory is relevant only in patients who were subject to surgical intervention. It is believed that endometriosis may develop in tissues directly involved with surgery or a wound, i.e. caesarean section scars and episiotomies or after tubal ligation or hysterectomy. Clinical symptoms and signs for scar endometriosis include a painful scar during the menstrual cycle and cyclic bleeding from the scar (112).

1.2.2.7 The genetic theory

Various studies have reported the possibility of correlation between endometriosis and gens due to its familial prevalence. A study showed that the occurrence of endometriosis is seven times greater in first degree relatives of the affected women compared to a healthy population (113). Patients with family history may also suffer more severe forms of endometriosis than those without it (114). Several other studies have looked at many genes that might be involved in this disease (115). Some of those candidate genes were Galactose-I-Phosphate Uridyl Transferase, Phase I and Phase II detoxification genes such as CYPIAI, NAT2 and GSTs, NAT2 respectively, steroid related genes, intracellular adhesion genes, angiogenesis and tumour suppressor genes. Due to the multiple genetic possibilities, it is believed to be a polygenic/multifactorial inheritance disorder. However, no specific gene has been clearly identified as the causative one. More studies are needed to clarify the role of each gene in the pathogenesis of endometriosis (115).
Environmental factors

An association between endometriosis and exposure to environmental contaminants has been explored in human and animal studies and it was suggested that they play a role in the pathophysiology of endometriosis (116). For example, it was found that endometriosis is more common among obese women and those with increased alcohol consumption. Endometriosis is an oestrogen dependant condition and both of which favour increased circulating levels of oestrogens (117, 118). On the other hand an interesting study published in 2009 by Killick looked at the effects of changes in lifestyle such as contraception method, smoking, alcohol, and caffeine intake on subfertility in general in patients attending an antenatal clinic. It showed that although the changes were towards better and healthier lifestyle, they did not have an impact on the prevalence of subfertility levels and did not lead to a reduction of such incidence (119).

Altered cellular immunity and inflammation

A great number of studies suggest that the peritoneal fluid in patients with endometriosis contains an increased number of activated macrophages that secrete various growth factors. Also, high levels of inflammatory cytokines, malformed immune cell function and a larger number of immune cells have been found in those patients (120). It is not clear whether this involvement is a primary response that leads to introducing and supporting the progression of endometriosis
or a secondary response to the ectopic endometrial growth in an effort to regulate the body physiologically (121).

Many studies have also looked for evidence which links specific genes associated with inflammation to endometriosis. There have been conflicting results and such association has not been confirmed so far (121).

1.2.3 Prevalence of endometriosis

The information about the prevalence of endometriosis in the general population published so far is not conclusive, this is due to the fact that endometriosis cannot be confirmed without direct visualisation of the lesions by laparoscopy or laparotomy.

One study showed that 6–10% of women in the general population, and 20% of women who have had a laparoscopy to investigate infertility, were diagnosed with endometriosis (122). The prevalence rate of endometriosis proven by laparoscopy in patients with chronic pelvic pain can range from 4-65%; and has been found incidentally in about 1-22% of women submitted to gynaecological surgery for other indications (123).

1.2.4 Symptoms

The main symptoms associated with endometriosis are recurrent painful periods, painful intercourse, and painful defecation during menstruation days, chronic lower abdominal pain and chronic lower back pain. Furthermore, endometriosis is often
associated with infertility (123, 124). The clinical presentation may include the presence of pelvic mass, however, typical lesions have also been found in asymptomatic women (125). The correlation between these symptoms and the stage of endometriosis is poor. With mild cases, patients frequently complain of severe pains and vice versa (126, 127).

What is important is that the patients with endometriosis may report having gastrointestinal symptoms like constipation, diarrhoea, having bright red stools from the rectum and melina. They can also present with genitourinary symptoms such as haematuria, dysuria, frequency and urgency (128).

### 1.2.5 Diagnosis

A detailed history of gynaecological symptoms must be taken. Pelvic examination must also be carried out in females of productive age complaining of recurrent dysmenorrhoea or pelvic pain. The pain is usually associated with menstruation. These symptoms can also be found in pelvic infection, early pregnancy, ectopic pregnancy, ovarian cyst torsion, appendicitis and IBS (129, 130).

Laparoscopy is the only diagnostic test that can reliably rule out endometriosis. It is also accurate in detecting endometriosis and was called the “Gold Standard Diagnostic Test” that is classified as the typical investigation for this condition (129, 131). Transvaginal ultrasound and magnetic resonance imaging (MRI) may be used to detect endometriosis especially in diagnosing deep infiltrating lesions, advanced endometriosis and cysts (132). CA125 serum levels can also be
measured as a laboratory marker. However, it is only elevated in the advanced stages of endometriosis and hence cannot be used as a screening for the disease (132).

Consequently, diagnosing and staging of endometriosis depends on clinical judgment, imaging techniques, surgical and histological evaluation.

### 1.2.6 Staging

Endometriosis is categorised into four main stages as defined by the American Society of Reproductive Medicine (133). The stage of the disease is decided according to location and spread of the disease, involvement of pelvic organs and degree of fallopian tube occlusion. The main stages are: minimal, mild, moderate, and severe.

The extent of the disease however, does not always correlate with the scale of symptoms (126, 132). Women with mild endometriosis may suffer more pain and symptoms than those with advanced stages, as asymptomatic women have been diagnosed with Stage 4 on laparoscopy for sterilisation (134). Figure 2 illustrates examples of endometriosis stages.

**Stage 1: Minimal endometriosis**

Only a few superficial endometriosis lesions situated on one ovary, peritoneum or uterosacral ligaments.
Stage 2: Mild endometriosis

Several small implants, superficial lesions on two or more of the above or involvement of one of the ovaries.

Stage 3: Moderate endometriosis

Ovarian cyst, deeper involvement of lesions, adhesions and scarring. The implants in stage three must be both superficial and deep. There must also be several prominent areas of scar tissue or adhesions.

Stage 4: Severe endometriosis

Deeply invasive lesions and / or severe adhesions. Patients with stage 4 endometriosis have many superficial and deep implants as well as large adhesions.
Figure 3 Examples of extent and location of endometriosis.

Adapted from the Revised American Society for Reproductive Medicine Classification of endometriosis (1996).
1.2.7 Pain in endometriosis

It is believed that deeply infiltrating endometriosis (DIE) might be responsible for severe chronic pelvic pain symptoms. This is due to compression, stretching of the peritoneum or infiltration of the nerves in the sub-peritoneal pelvic space by the implants or adhesions. Anatomical locations and the involvement of organs may also play a role in the type of pain in DIE (135). However adhesiolysis, surgical and hormonal treatment and presacral neurectomy, did not relieve chronic pelvic pain in patients, with the exception of those with severe endometriosis (136-138) an indication that there are some other factors. Inflammation and pelvic congestion also cause hypersensitivity and pelvic pain in these patients. Yet, anti-inflammatory drugs (NSAIDs) showed to have a little effect on pain relief (139). It is also believed that central sensitisation and neural mechanisms may also contribute to pain in endometriosis (140, 141). Pain mechanisms in endometriosis seem to be of a complex nature and more research will lead to a better understanding of this area.

1.2.8 The role of Prostaglandins and Inflammation

Research showed a direct relation between pain in endometriosis and prostaglandins (PGs) (142). As mentioned before many theories have been put forward to try to explain the pathogenesis of this condition. Some research explored the role of prostaglandins, it is well known that the peritoneal fluid of patients with endometriosis contains a higher level of prostaglandin compared to
patients without this condition (143, 144). Anti-inflammatory drugs have been used in treating the pain associated with endometriosis and were shown to work in some occasions (142).

However, there is no exceptional new treatment so far that can completely treat endometriosis or prevent its recurrence.

Researchers are increasingly becoming interested in the role in prostaglandins in endometriosis as they may play a major role in different pathophysiological features of endometriosis such as cell proliferation, angiogenesis and immune suppression. Prostaglandins in the peritoneal fluid are produced by some peritoneal macrophages and ectopic endometriotic tissues (144).

Proinflammatory cytokines can be associated with the endometrial tissue passing through the fallopian tubes to the peritoneum, as suggested in the retrograde theory. These cytokines cause chronic inflammation in the pelvic cavity. Such inflammation usually triggers macrophages and other immune cells. These then become hyper active after being stimulated in the peritoneal fluid. Macrophages work on getting rid of the endometrial tissue that had migrated to the peritoneal cavity (145). Endometrial retrograde migration is very common in women but it is expected that this defending mechanism prevents these women from developing endometriosis.

However, when this fails, macrophages will not clear all migrated endometrial cells to the peritoneum cavity and endometriosis cells can then be implanted in the
abdomen causing endometriosis. It is believed that prostaglandin E2 plays a major role in suppressing the capability of macrophages in clearing the endometriosis cells, (145).

Figure 4 summarises the role of prostaglandins in endometriosis. According to the retrograde theory, the endometrial cells pass through fallopian tubes to the peritoneum and cause chronic inflammation. Macrophages and some other immune cells are recruited as a response to the inflammation. They usually secrete matrix metalloproteinase-9 (MMP-9) to destroy the extracellular matrix and break up the endometrial tissues. In addition, the receptor CD36 is highly expressed in the plasma membrane of macrophages to facilitate phagocytosis of these small fragments of endometrial remains. However, high concentration of PGE2 suppresses the expression of MMP-9 and CD36. This significantly inhibits the ability of macrophages to tackle endometriosis. As a result, the endometrial tissues can be implanted and proliferate in the peritoneal cavity (145).
Figure 4 Prostaglandins and endometriosis.

The figure illustrates how prostaglandin E2 suppresses the phagocytosis by macrophages leading to endometriosis. The figure was taken from a paper published in 2012 by Wu MH et al. (145).
1.2.9 Treatment

1.2.9.1 Medical Treatment includes

Medical treatment is the first line in managing endometriosis (99).

1. Non-steroidal anti-inflammatory drugs (NSAIDs) such as Ibuprofen.
   However there isn’t enough evidence that NSAIDs are efficient in treating endometriosis pain (146).

2. Oral Contraceptives: there are many different types and they contain mainly Oestrogens and Progestogens.

3. Progestogens: These are synthetic Progesterone like Medroxyprogesterone acetate oral or depot injection (147). The disadvantage of this treatment is that it cannot be used in patients who are planning for pregnancy, as it suppresses the ovaries.

4. Testosterone derivatives or synthetic androgens: such as Danazol (148) or Methyltestosterone. Although some research showed that such treatment helped with pain, it became unpopular because of side effects when used orally. Some of those side effects are irreversible deepening of the voice, hirsutism and acne (149).
5. Antiprogesterone tablets: (100) suppress the release of progesterone and oestrogen by the ovaries that may lead to abolition of the menstrual cycle. These agents interact with their receptors in the Thalamus that leads to a decrease in the secretion of LH and FSH. This type of treatment also cannot be used for patients who wish to become pregnant.

6. Gonadotropin-releasing hormone (GnRH) agonists, for example Leuprolide for 4 weeks or Nafarelin 1 puff twice a day intranasal spray or monthly injection (intramuscular, subcutaneous). It is also available as an implant. These agonists work by down regulating the release of oestrogen and progesterone that may lead to side effects of menopausal symptoms and bone density loss. GnRH agonist plus, is GnRH agonists plus oral contraception or low dose of Progestogenic agents to avoid the latter problem of osteoporosis (99)

1.2.9.2 Surgical treatment

Laparoscopy

Laparoscopy is widely used in this field, not only to confirm the diagnosis but also to provide treatment. Endometriosis lesions that are found during laparoscopy, are usually eradicated immediately following confirmation of the disease at the time of intervention (150) and adhesions that may cause infertility are separated by adhesiolysis (100). Surgical removal, endocoagulation or laser treatment are used to destroy endometriotic lesions during laparoscopy (99). People of a younger age
tend to have low grade endometriosis and it is frequently noted that their symptoms do not completely disappear after surgical treatment. Associated diseases such as irritable bowel syndrome and lactose intolerance must be considered in these patients. They need to be seen by a gastroenterologist if their symptoms are focused in the gastrointestinal system, or by a urologist if their symptoms are related to the urinary system (99).

Other treatments that are applied during laparoscopy include unipolar or bipolar cauterisation and laser ablation using CO2 and KTP, Aluminum and Nd:YAG lasers (151).

**Laparoscopic uterosacral nerve ablation (LUNA):**

Women with recurrent dysmenorrhea may benefit from this procedure. This technique disrupts the nerve fibre, however, some studies showed that it does not have an advantage over conservative surgery in terms of relieving pain (152).

**Presacral neurectomy**

This is a surgical procedure that attempts to relieve chronic pelvic pain (153). It disrupts sympathetic enervation to the uterus at the superior hypogastric plexus. Some studies have shown that women who underwent such treatment along with laparoscopic surgery reported better improvement in their symptoms compared with females who received laparoscopic surgery alone. However, this procedure is quite risky and bleeding is one of its major complications.
Hysterectomy

Total Abdominal Hysterectomy with bilateral salpino-oophorectomy (TAH-BSO) is usually offered to patients who have severe symptoms due to endometriosis, where all other treatments have failed and where the severity of the disease is far more than the desire to maintain fertility. It is not usually performed in women of reproductive age because of its effects, as lack of female hormones has an effect on bone density, sexual drive and the vaginal mucosa. Oophorectomy leads to the elimination of the disease and to surgical menopause causing atrophy of endometrial tissue (151).

1.2.9.3 Combined Surgical and Medical Treatment

Medical therapy is often used before surgery as it may reduce the size of endometriotic lesions and decreases blood loss during and after surgery. It is also used after surgery for lesions which were inoperable because of their location or size (154). This model of treatment also helps to prevent the recurrence of endometriosis or symptoms (155).

1.2.10 Adenomyosis

Endometriosis and adenomyosis are both oestrogen-dependent diseases (156). Adenomyosis is the implantation of endometriotic lesions in the myometrium of the uterus (157). It affects adult women who are usually multiparous (158) and
between the age of 30 and 50 (156). Adenomyosis is significantly associated with peritoneal endometriosis (159).

The pathophysiology is poorly known and the theories which have been put to explain it are similar to those of which have been linked to endometriosis. Some of these theories are angiogenesis (160, 161), hormonal (162) genetics (163), inflammatory factors (164) and mechanical or physiologic trauma (165). Patients with adenomyosis may not show any symptoms. However, some patients might report dyspareunia, heavy menstrual bleeding and dysmenorrhea (166).

Many research studies have been done on endometriosis compared to a few on adenomyosis. The prevalence of this condition is variable (156) and difficult to diagnose. MRI and ultrasound might be useful for diagnosis. However, the most accurate way for diagnosing adenomyosis is histopathology after hysterectomy.

Due to the complexity of diagnostic procedures, time frame of the study and financial costs, it was not possible for us to address adenomyosis in this study.
Figure 5 Illustration shows adenomyosis located in the myometrium.

The figure was taken from The Institute for Female Alternative Medicine and published by Dr. del Junco Jr, Valley Presbyterian Hospital, California.
1.3 BLOATING AND DISTENSION:

Although bloating can occur in people without any abdominal pathology, it is relatively uncommon in the normal population (167-169).

However, bloating, which is the sensation of increased pressure within the abdomen, is an extremely common symptom in patients with IBS and typically it is absent or mild in the morning and gradually gets worse during the course of the day, especially after meals, and is usually at its worst in the evening. It is estimated that up to 90% of IBS patients suffer from bloating with women tending to be more affected by bloating than men (170, 171) and it is not infrequently ranked as the patient’s most disturbing symptom (172). Many patients who complain of bloating also claim that their abdominal girth increases at the same time and it has been shown that approximately 50% of patients with bloating also exhibit significant increases in girth which is usually referred to as distension and this can now be objectively measured by abdominal inductance plethysmography (173, 174). However, patients and most doctors use the terms bloating and distension synonymously, and actually bloating is the most common identifier. This was not that important until it became possible to measure distension objectively and it became clear that the pathophysiology of bloating and distension is not exactly the same (170, 173).
The evaluation of bloating and distension has been greatly advanced by the development of techniques such as the gas challenge technique (17, 175), abdominal and diaphragmatic electromyography (176, 177), CT scanning (178), and abdominal inductance plethysmography (174, 179). It seems likely that MRI scanning may also be a useful tool in this field in the future.

Many mechanisms have been put forward to explain bloating such as psychological stress, weak abdominal muscles, excessive gas production, disordered motility and visceral hypersensitivity (180-182).

### 1.3.1 The role of gas in bloating and distension

There are three main sources of gas production in the intestinal system. The first one is called “aerophagia” which comes normally from swallowed air, the second is by the process of bacterial fermentation and the third is as a result of chemical reactions. It might be considered that excessive gas could be the cause of bloating and distension in patients with irritable bowel syndrome. However, most studies have not shown patients with IBS to have excessive amounts of gas retained within their gut (168). Despite this observation, Azpiroz and colleagues have conducted a series of experiments clearly showing that gas transit is abnormal in patients with IBS (17). When gas is infused into the jejunum of controls and patients with IBS those with IBS retain more gas than controls. This delayed gas transit can be improved by exercise (183) or the administration of a prokinetic agent such as Neostigmine (184).
There is increasing interest in the role of the microbiota in IBS and there is no doubt that the gastrointestinal flora is also closely involved in gas metabolism. Therefore, it seems reasonable to assume that the microbiota may also contribute to bloating or distension and some trials of probiotics have shown that these products can in fact improve both bloating and distension (185, 186).

1.3.2 Weak abdominal muscles

It might be considered that abdominal distension may partly be explained by weak abdominal musculature. This has been addressed in a small study comparing the ability of IBS and control patients to do sit ups (187). The IBS patients were found to be less able to do sit ups than controls. This finding supports the idea that weak abdominal muscles may contribute to distension. However, this work has never been replicated although it would be interesting to see whether strengthening abdominal muscles did lead to any improvement in distension.

1.3.3 Disordered motility

As previously stated, there is somewhat conflicting evidence about the role of motility in irritable bowel syndrome and therefore, it is not surprising that there are no convincing studies implicating motility in the pathophysiology of bloating and distension. However, Azpiroz and colleagues have speculated that gastrointestinal tone may be important in gas transit and this deserves further investigation (188, 189).
1.3.4 Visceral hypersensitivity

Visceral hypersensitivity is a common finding in patients with IBS and it has been postulated that this abnormality might contribute to the sensation of bloating. This question has been addressed in a study by Agrawal and colleagues where patients with bloating without distension or bloating with distension were assessed for visceral hypersensitivity using a barostat (182). It emerged that patients with bloating on its own were far more likely to be viscerally hypersensitive than those with bloating and distension.

1.3.5 Constipation and transit

The contribution of bowel habit and transit have been addressed in patients with bloating and distension and it has been shown that bloating tends to be associated with a loose bowel habit whereas distension is more commonly associated with constipation or delayed transit.

1.3.6 The abdominal accommodation

It has been speculated that there must be some form of accommodation reflex to allow an increase in abdominal contents, such as that following a meal, to be accommodated within the abdomen without a significant change in the shape of the abdomen. The anterior abdominal wall and the diaphragm are the only structures that could be involved in this process as all the other walls of the abdominal cavity are fixed. This possibility has been assessed by a combination of
CT scanning and diaphragmatic electromyography using the insufflations of gas into the rectum as a way of increasing intra-abdominal volume (190). Using these techniques has been shown that the normal response to an increase in intra-abdominal volume is contraction of the anterior abdominal muscles and relaxation of the diaphragm so that it becomes elevated. However, in IBS this reflex is completely reversed so that the diaphragm contracts and the abdominal muscles relax and this must explain some cases of abdominal distension (190). As constipation tends to be more associated with distension than bloating it could be that by occupying more space a loaded colon in a patient with IBS could be stimulating this abnormal reflex.

1.3.7 Menstruation and bloating

Even normal females can experience a change in bowel habit around the time of menstruation. However, these effects can be more pronounced in patients with IBS and can give rise to both upper and lower gastrointestinal symptoms (191). Jackson, et al. reported that between 40%-66% of female IBS patients complain of worsening of bloating and distension few days before menstruation (192). The mechanisms involved in the production of these symptoms are not entirely clear but changes in levels of sex hormones and prostaglandins are possible explanations. To date no objective studies of abdominal distension during the menstrual cycle have been undertaken but such research would be of interest.
1.3.8 Conclusion

It, therefore, appears that bloating and distension have slightly different underlying mechanisms with bloating being more associated with abnormal gas handling, visceral hypersensitivity, diarrhoea and possibly an abnormal gut flora, whereas distension is associated with weak abdominal musculature an abnormal accommodation reflex, constipation, slow transit and an abnormal gut flora. This obviously has implications for treatment suggesting that targeting visceral hypersensitivity might help bloating whereas speeding up transit or relieving constipation might help distension.

1.4 HYPOTHESIS AND AIMS

1.4.1 Background

The overlap between gynaecological and gastroenterological symptoms can be clinically challenging and this is a particular problem in relation to endometriosis and IBS. These two conditions share many symptoms making it difficult on occasions, for the clinician to decide on the best management approach. This dilemma is even more problematic in a patient who is found to have minimal to mild endometriosis but also appears to have symptoms consistent with a diagnosis of IBS. It was the purpose of this research to try and establish whether there was any symptom based approach or investigation (barostat testing or plethysmography) that might help to lead to better management approaches to this situation.
1.4.2 Aims

1. To assess visceral sensitivity using barostat testing in endometriosis, IBS, laparoscopically negative abdominal pain, and patients attending for laparoscopy sterilisation as a control for the possibility of laparoscopy itself resulting in sensitisation.

2. To compare demographic features, abdominal symptoms, quality of life, psychological status, non colonic symptomatology in the same group of participants.

3. To compare abdominal bloating and distension in patients with endometriosis and IBS
CHAPTER TWO: THE ROLE OF VISCERAL SENSITIVITY IN IRRITABLE BOWEL SYNDROME AND ENDOMETRIOSIS
2.1 BACKGROUND

Visceral sensitivity has been increasingly recognised recently as one of the mechanisms underlying the pathophysiology of functional bowel disorders. The most detailed evidence has been obtained in patients with irritable bowel syndrome (22).

There is evidence that patients with IBS are more viscerally sensitive to luminal distension of the gut than controls (30, 193). This was suggested by many researchers after the initial report by Ritchie back in 1973 (11). Previous reports showed that visceral sensitivity might be a biological marker for IBS and that the intensity of symptoms and the level of hypersensitivity were linked (30) thus giving the potential for differentiating the symptoms of this disorder from other conditions (32). There are, however, no data about visceral sensitivity in patients with endometriosis and this study was designed to look at this area.

It is possible that visceral hypersensitivity might be the reason behind the symptoms in patients with endometriosis especially those with minimal to mild disease. Therefore, reducing the sensitivity in endometriosis patients might help in controlling their pain.

It is possible that in many patients, treating the IBS or the visceral hypersensitivity may prevent a whole range of unnecessary gynaecological interventions which
could actually make their IBS even worse as any intervention with the abdomen nature such as laparoscopy or surgery leads to worsening of IBs symptoms. However, in others the endometriosis may need targeting and it would be useful to have a method of identifying such individuals. The results of this study should help to clarify whether, by carefully recording gastrointestinal symptoms or simply measuring visceral sensation in these patients, it might be possible to identify the correct treatment pathway.

2.2 AIM AND OBJECTIVES

The aim of this project is to assess visceral sensitivity to balloon distension in patients with endometriosis.

The objectives are to establish whether visceral hypersensitivity may explain why some patients with very mild endometriosis are so symptomatic.

2.3 HYPOTHESIS AND PROOF OF CONCEPT

Because IBS and endometriosis are relatively common it is likely that the two conditions will often co-exist. There has been an interest in the overlap between IBS and endometriosis for some time (130, 194) and speculation that the visceral hypersensitivity associated with IBS might make these patients more likely to feel pain, even with minor endometriosis, which would not trouble other individuals. Alternatively, the symptoms of their IBS might be leading to gynaecological investigation and detection of endometriosis which is actually asymptomatic. We
feel these questions can be addressed by a detailed investigation of the relationship between visceral sensation and symptoms in both IBS and endometriosis patients.

2.4 EXPERIMENTAL DESIGN

2.4.1 Ethical approval

The study was approved by the South Manchester Research Ethics Committee and all participants gave written informed consent, Research Ethics Committee Reference Number 03/SM/190 dated 19 April 2007.

2.4.2 Power calculation

It was estimated that this study required twenty patients in each of the five groups recruited. These were 20 women with minimal to mild endometriosis, 20 with moderate to severe endometriosis, 20 with laparoscopy negative abdominal pain, 20 asymptomatic female controls undergoing laparoscopic sterilisation and compared with 20 women with IBS.

This was based on a power calculation using previous data collected in our laboratory on visceral sensation using rectal sensitivity testing. This calculation allows an 80% power to detect a difference in sensitivity of 10 mmHg between groups at a significance level of 5%.
2.4.3 Statistics

Comparisons between patients’ groups were carried out using one-factor ANOVA followed by the Scheffe’s multiple comparison tests. The relationship between pain thresholds and IBS severity scores as well as endometriosis pain scores were assessed using the Pearson correlation coefficient. Pain thresholds were compared in patients with ROME positive and ROME negative endometriosis using the independent t test. The same statistics were used for comparing endometriosis pain scores in patients with minimal to mild and moderate to severe endometriosis.

2.4.4 Recruitment

The gynaecological department has a very busy laparoscopic unit used by five consultant teams all of whom kindly collaborated with us. It was estimated that it is possible to recruit three patients per week. However, a large number have been contacted with regard to this project and nearly less than 50% of those replied enquiring about it. Not everyone showing interest in the study was eligible and many of these did not fill in the inclusion criteria. Patients were contacted in order to arrange visits and times for both the barostat and the belt visit.

The results of the sensitivity testing were then correlated with the symptomatology of the various patient and control groups to see if the hypothesis was supported or not.
Patients identified from information supplied by the coding department concerning patients who have attended the hospital in the past for a laparoscopy were also invited to take part in the study.

As well as recruiting patients from the gynaecological department and the coding department at South Manchester University Hospital. Patients from outpatient clinics and from our volunteer pool were invited to take part in our research. Ethically approved adverts were displayed in the Hospital, University and at GP surgeries. Global emails were also often sent to UHSM staff.

**2.4.5 Inclusion Criteria**

1. All patients in the endometriosis groups were given a diagnosis of endometriosis confirmed at laparoscopy, and graded as minimal, mild, moderate or severe. Other patients were given a diagnosis of IBS. Patients with negative laparoscopy for abdominal pain were also included.

2. All patients in the endometriosis, IBS and negative laparoscopy abdominal pain groups had pelvic ultrasound before laparoscopy. Only those with no clinically significant abnormalities were included.

3. Ability and willingness to communicate well with the investigator and to comply with the requirements of the study, including the completion of the patient’s diary.

4. Written informed consent to participate in the study.
2.4.6 Exclusion Criteria

1. Known history of significant and/or inadequately controlled cardiovascular, respiratory, renal, hepatic, gastrointestinal (e.g. inflammatory bowel disease), haematological, neurological, psychiatric, gynaecological disease (other than endometriosis) or other disease likely to compromise the patient’s ability to participate in and complete the study.

2. Functional disorder of the upper G.I. tract, which is more prominent than their irritable bowel syndrome.

3. Use of medication which may have an effect on gut sensitivity or motility taken within 48 hours of the sensitivity test.

4. Ingestion of caffeine or smoking within 24 hours of the study day.

5. Women who are pregnant or breast-feeding.

2.5 STUDY METHODOLOGY

Patients attending the gynaecological department for the laparoscopic investigation of abdominal pain and found to have endometriosis were eligible for study. Those without any evidence of co-existent disease had their endometriosis graded according to the Revised American Fertility Society Guidelines (195, 196). Subjects identified from other sources which have been mentioned under recruitment paragraph (2.4.4 ) have also been included. Patients were then divided into two
endometriosis groups of 20 patients each: minimal-mild and moderate-severe. For the purpose of comparison, women attending for laparoscopic sterilisation were included as a group of laparoscopically normal healthy volunteers in order to investigate the possibility that laparoscopy might lead to visceral sensitisation. 20 patients attending for diagnostic laparoscopy to investigate abdominal pain and who were found to have a normal pelvis were also asked if they were prepared to participate and they formed a group of laparoscopically negative abdominal pain individuals. A final fifth group consisted of patients who have been diagnosed with IBS.

Participants taking long term medication likely to affect visceral sensation were excluded as were those unable to stop taking, for a period of 48 hours, any other medication that could possibly interfere with the results. All Barostat tests were carried out in the Luteal phase of the menstrual cycle in those individuals with regular periods.

### 2.5.1 The barostat

A barostat is a pneumatic device which is a system using compressed air to do work. It is used to inflate an intraluminal balloon through a sequence of isobaric pressure levels and allows for indirect measurement of variations of pressure and volume during distensions. The Balloon is placed in the rectum and attached to the barostat machine. The barostat is attached to a host computer that is equipped with the Windows operating system. Both pressure and volume readings from the
barostat are collected by this host computer and stored in a file for later analysis. This means that a computerised record of the test is recorded and the file can be viewed later using a standard spreadsheet programme.

The operating system (the software) controls the barostat by issuing a sequence of commands via the serial port of the host computer. These commands can be activated by the investigator through the computer mouse, in addition to some function keys on the host computer.
Figure 6 A picture of the Barostat machine.

The figure shows a barostat, the host computer and two keypads which are placed next to the machine. The picture was taken in our laboratory of the barostat machine used for this study. The balloon was attached for illustration purposes.
Assessment of rectal sensitivity was carried out using a tracking barostat technique as follows. After an overnight fast and fleet enema was administered in the morning of the test to clear the rectum from any stool before a barostat flaccid bag attached to a catheter was placed in the rectum. This was followed by a one hour recovery period. Basal operating pressure (BOP) was then assessed by increasing the pressure in the bag in 1 mmHg increments until respiratory artefact was observed or 12 mmHg was reached. Following this, isobaric phasic distensions were performed (increments of 4 mmHg for 1 minute with 1 minute return to BOP in between) up to a maximum pressure of 48 mm Hg. At each step, the volume of the bag was measured in order to build compliance curves. The patient was then questioned at each inflation step (4 mmHg) in order to find the amount of distension associated with (1) the first sensation of distension, defined as the pressure at which the patient experiences the perception (score = 1 and 2) of the pressure including the first painful sensation (score = 2) see below.

During each inflation from BOP levels, at 30 seconds after commencement of the inflation, patients were prompted to indicate on a standard pro forma whether they were experiencing either the sensation of “stool” or “pain/discomfort”. For each of these, they were required to score the level of sensation using the scales below:

<table>
<thead>
<tr>
<th>Stool sensation</th>
<th>Pain/Discomfort</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 = no sensation</td>
<td>0 = no pain/discomfort</td>
</tr>
<tr>
<td>1 = first sensation</td>
<td>1 = mild but not sustained pain/discomfort</td>
</tr>
</tbody>
</table>
2 = constant sensation / gas  2 = mild but sustained pain/discomfort
3 = need to defaecate  3 = moderate pain
4 = urgent need to defaecate  4 = intense pain

Tracking, which is a technique which makes the inflations unpredictable to the subject and thus minimise bias, was commenced when the subject first experienced moderate pain (score = 3).

Subsequent distensions were then adjusted up or down, depending on the subject’s response to the previous distension: if the subject reported pain on the previous trial, the next distension was decreased or kept the same; if the subject reported no pain on the previous trial, the next distension was increased or kept the same. In order to make the changes in amount of distension unpredictable, a random numbers algorithm was used to decide whether to decrease the amount of distension or keep it the same following a painful test trial. The sensory threshold was taken as the average intensity over a series of trials on which one tracks (i.e. makes adjustments that are slightly above and slightly below) the threshold.

The distension test was stopped after 12 distension trials or after reaching the upper limit of 48 mmHg without pain sensation. At any time, the patient was able to discontinue the distension session, for any reason, by pressing the “panic button”. The investigator was also able to stop the test whenever it seemed to be necessary (197).

Full Barostat operation procedure is attached in appendix 8.6 including patient’s preparation and machine calibration.
Figure 7 Picture of a Barostat balloon

This picture shows a Single-Use Barostat Catheter including the balloon which was used for the barostat tests. The picture was taken at the Neurogastroenterology Unit, Wythenshawe Hospital.

2.5.2 Barostat operating procedure

Patients were reminded to fast overnight and abstain from caffeine, alcohol, smoking and strenuous exercise, for 24 hours beforehand, to avoid any effects on the bowel before performing the barostat test. All volunteers received a fleet enema which was administered on the morning of the procedure either at home or in the Neurogastroenterology Unit at Wythenshawe Hospital. They were asked to rest for approximately 20 minutes to half an hour after they had emptied their bowels to allow the gut to relax.
During that time, the computer then the barostat machine was switched on to warm up for approx 1 hr prior to use. Patients were reminded again with what the test involves and a full explanation about it was given and all their questions were answered. The catheter was then inserted after performing PR examination to check for any abnormality. The catheter tubes were left disconnected for approximately 30 minutes after catheter insertion and before the barostat test was started. While the patient was relaxing, the machine was calibrated (Appendix 8.6 for full details).

2.6 RESULTS

The data derived from the barostat testing for first sensation, stool sensation, pain sensory thresholds and compliance was analysed.

All groups were comparable with respect to age with no significant difference emerging. These data are detailed in full in Table 16. With regard to sensory threshold, differences did emerge and these are detailed in Table 1 and represented graphically in Figure 8, 9, 10, 11, 12 and 13. As can be seen, compared to laparoscopy controls all groups tended to be more sensitive for first sensation and stool sensation and by the time pain thresholds were reached. There was a highly significant difference with respect to the endometriosis groups with patients with minimal to mild endometriosis and moderate to severe endometriosis exhibiting hypersensitivity. IBS patients also exhibited hypersensitivity as might be expected and the laparoscopy negative abdominal
pain group showed a trend toward hypersensitivity although this did not show any significance. There were no differences with respect to compliance.

A 90% normal reference range for sensitivity was derived for laparoscopic controls and found to be 31-48 mmHg and based on this, 60% (12 / 20) of the patients with minimal to mild endometriosis and 65% (13 / 20) of those with moderate to severe endometriosis had pain thresholds below the lower limit of this range. In addition, 75% of the patients in the IBS group and 45% of patients in the laparoscopy negative pain group also had sensitivity below this range.
### Table 1 Visceral sensitivity in groups studied

The table illustrates the visceral sensitivity data in all five groups of participants. As can be seen, there are significant differences in pain threshold pressures between both endometriosis groups and healthy volunteers called laparoscopy controls. IBS patients had similar levels of pain threshold to the endometriosis groups. Comparison with controls: *p<0.001; ‡ p=0.05; # p=0.001; † p=0.002

<table>
<thead>
<tr>
<th></th>
<th>Laparoscopy Controls (n=20)</th>
<th>Minimal-Mild Endometriosis (n=20)</th>
<th>Moderate-Severe Endometriosis (n=20)</th>
<th>Laparoscopy Negative Abdominal Pain (n=20)</th>
<th>Irritable Bowel Syndrome (n=20)</th>
<th>Comparison of Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First sensation</strong></td>
<td>19·2 (16·3,22·1)</td>
<td>15·3 (14·0,16·6)</td>
<td>15·5 (13·6,17·4)</td>
<td>16·3 (14·1,18·5)</td>
<td>12·6 (10·8,14·4)*</td>
<td>p&lt;0·001</td>
</tr>
<tr>
<td><strong>Stool sensation</strong></td>
<td>32·6 (28·6,36·6)</td>
<td>25·9 (23·6,28·2)</td>
<td>26·0 (21·9,30·1)</td>
<td>28·0 (22·8,33·2)</td>
<td>24·3 (20·4,28·3)†</td>
<td>p=0·027</td>
</tr>
<tr>
<td><strong>Pain threshold</strong></td>
<td>39·5 (36·0,43·0)</td>
<td>28·1 (24·5,31·6)#</td>
<td>28·8 (24·9,32·6)†</td>
<td>32·7 (28·8,36·6)</td>
<td>25·4 (21·7,29·3)*</td>
<td>p&lt;0·001</td>
</tr>
<tr>
<td><strong>Static compliance</strong></td>
<td>6·4 (4·9,7·9)</td>
<td>5·6 (4·4,6·8)</td>
<td>7·2 (5·7,8·8)</td>
<td>8·1 (5·0,11·2)</td>
<td>8·3 (6·6,10·0)</td>
<td>p=0·18</td>
</tr>
<tr>
<td><strong>Dynamic compliance</strong></td>
<td>7·1 (5·7,8·6)</td>
<td>7·1 (5·9,8·2)</td>
<td>8·4 (7·3,9·6)</td>
<td>8·3 (6·2,10·4)</td>
<td>9·1 (7·8,10·5)</td>
<td>p=0·18</td>
</tr>
</tbody>
</table>
The thresholds for first sensation scores were compared in patients with minimal to mild, moderate to severe endometriosis and compared with laparoscopy controls, laparoscopy negatives and IBS. Minimal-Mild, Moderate-Severe endometriosis and IBS had lower levels of first sensation thresholds compared to Laparoscopy controls. However, the levels only reached significance in IBS patients.
Figure 9 Stool sensation

Stool sensation levels were similar between Laparoscopy Controls, Minimal to Mild, Moderate to Severe endometriosis and laparoscopy Negative Abdominal Pain groups. Only patients with IBS had significantly lower levels of stool sensation compared with other groups (P value, 0.05).
Figure 10 Pain threshold in all five groups.

Pain thresholds in Minimal-Mild and Moderate-Severe endometriosis were significantly lower than HV laparoscopy controls (p=0.001; p=0.002 respectively). Both groups had pain threshold levels or hypersensitivity similar to that seen in IBS, which was significantly different from controls (*p<0.001). Patients with the Laparoscopy Negative Abdominal Pain did not differ significantly from other groups although pain thresholds were lower than controls.
Figure 11 Pain threshold differences in endometriosis compared to control groups.

The figure shows a graphical representation of the highly significant difference in the thresholds for pain in the endometriosis groups compared to controls. This indicates that the process of having a laparoscopic procedure is not, in itself, the cause of the hypersensitivity observed in the other groups. A 90% ‘normal’ reference range for sensitivity is presented on the graph. This was derived for the laparoscopic controls and found to be 31-48 mmHg.
Figure 12 Static compliance

There was no significant difference between groups with respect to static compliance
There were no differences in dynamic compliance between Laparoscopy Controls, Minimal to Mild, Moderate to Severe endometriosis, laparoscopy Negative Abdominal Pain and IBS groups.

Figure 13 Dynamic compliance.
2.7 DISCUSSION

These results show that patients with endometriosis exhibit visceral hypersensitivity which is nearly as extreme as that seen in patients with irritable bowel syndrome.

The laparoscopically normal healthy volunteers had sensory thresholds within normal limits according to previous research done at the unit and to the figures of pain thresholds available in the literature. This indicates that the process of having laparoscopy does not explain the finding of hypersensitivity in the endometriosis group. The laparoscopy negative abdominal pain patients exhibited a degree of visceral hypersensitivity and this is almost certainly explained by the fact that many of these patients met the ROME criteria for IBS (Table 8, Chapter Four). This would explain the hypersensitivity seen in these individual although it did not reach significance when compared to healthy volunteers.

The degree of hypersensitivity observed in the minimal to mild endometriosis group compared to the moderate to severe endometriosis group was not significantly different. Furthermore, the proportion of patients who exhibited visceral hypersensitivity was 60% and 65% for minimal to mild endometriosis and moderate to severe endometriosis respectively. Thus it appears that visceral hypersensitivity is equally prevalent and equally severe in the two endometriosis groups.
There are at least two possible explanations for hypersensitivity in patients with endometriosis. Firstly, the disease itself might in some way be sensitising the peritoneal cavity with this hypersensitivity extending to the gut in some way. Alternatively, it could be that these patients are suffering from irritable bowel syndrome which is well known to be associated with visceral hypersensitivity and that this hypersensitivity is not necessarily confined to the gastrointestinal system. There does not appear to be much data in the literature examining the possibility that endometriosis can lead to hypersensitivity but there is quite a lot of evidence that the hypersensitivity associated with irritable bowel syndrome can affect the whole gastrointestinal system (198). In addition patients with irritable bowel syndrome do exhibit auditory (199) and visual hypersensitivity (200) and IBS is often associated with fibromyalgia. Fibromyalgia is a condition where patients appear to have painful joints without any evidence of arthritis and some form of hyper sensitivity might be a possible explanation. Furthermore, bladder symptoms are very common in patients with IBS and are consistent with irritable bladder syndrome" (3, 201). Consequently, this suggests that the bladder is more sensitive in patients with IBS and there is some evidence to support this.

As discussed in Chapter one (section 1.1), there is a considerable interest in the role of inflammation in patients with irritable bowel syndrome. It is very common for patients with IBS to report the development of symptoms after an episode of gastroenteritis and more recently histological studies have suggested the presence of low grade inflammation in the gastrointestinal mucosa in patients with IBS. It is
therefore, interesting that inflammation is now the subject of interest in endometriosis raising another way that these two conditions could possibly be linked. It has been postulated that minor defects of the immune response might make some patients more susceptible to inflammation and this could have a genetic basis. It is noteworthy that both endometriosis and IBS have quite strong familial prevalence and there is continuing interest in the genetics of these two conditions.

The most exciting consequence of this piece of research is that it raises the possibility of a new approach to treating endometriosis. Clearly, severe endometriosis demands specific treatment whereas minimal to mild endometriosis is very challenging for gynaecologists to treat. These patients with mild disease appear to have symptoms out of proportion to the extent of their disease and these symptoms are very hard to treat. Consequently, it is tempting to raise the possibility that the hypersensitivity that has been demonstrated in these mild cases might in some way be amplifying the pain of their condition. Therefore, it may be worth considering treating the hypersensitivity with medication before embarking on more invasive treatments such as laser ablation or hormonal manipulation. Alternatively, if their pain is not related to their endometriosis but caused by irritable bowel syndrome, it still makes sense to try medical management which, in the case of irritable bowel symptoms, is very similar to that which is used for visceral hypersensitivity.
It would, therefore, be of considerable interest to undertake a study on the effect of a drug that might have a positive influence on visceral hypersensitivity, such as tricyclic antidepressants, in patients with mild endometriosis and visceral hypersensitivity.
CHAPTER THREE: ABDOMINAL BLOATING AND DISTENSION IN IRRITABLE BOWEL SYNDROME AND ENDOMETRIOSIS.
3.1 INTRODUCTION

It is well known that distension and bloating are common in patients with IBS although it is completely unknown what their actual prevalence might be in endometriosis. It is known that distension is related to delayed transit and constipation whereas bloating is associated with visceral hypersensitivity. It is, therefore, possible that as visceral hypersensitivity is common in endometriosis as discussed in Chapter Two, bloating might also be a feature of endometriosis.

Tape measuring combined with CT scanning have been used before, however, such methods cannot be used over a length of time (202). As abdominal inductance plethysmography is now available for the accurate and objective measurement of distension over a period of 24 hours, it was felt that it would be extremely useful to undertake a project assessing subjectively reported bloating and objectively measured distension in endometriosis and irritable bowel syndrome to establish whether the pattern of bloating and distension differs between these two groups (174).

3.2 AIM OF THE PROJECT

The aim of this research is to measure bloating and distension in IBS and endometriosis groups used in this research namely minimal to mild and moderate.
to severe endometriosis. The objectives are to find out if bloating and distension, which are features of IBS, are also common in endometriosis.

3.3 METHODS OF INVESTIGATIONS

Patients were asked to answer a question if they felt that they suffer from bloating or not and if so, to score the severity of their bloating on a linear analogue scale.

In order to measure distension, patients were asked to wear an Abdominal Inductance Plethysmography (AIP) belt (174, 179), to measure their abdominal girth for 24 hours. Previous studies have shown that there is no statistically significant difference between girth measurements taken in the standing and sitting positions (174). The distension measurements have been collected and analysed in all five groups recruited for this study. However, in a proportion of subjects, the belt failed for technical reasons or the patient was reluctant to either attend the initial belt visit or to return for a repeat study in case of a belt failure.

The data have been compared in 3 and 4 groups, after combining the two endometriosis groups. The total number of patients who had a valid distension belt data was 46. These included 20 IBS patients, 17 patients with minimal to mild endometriosis and 9 with moderate to severe endometriosis.

Volunteers taking long term medication that have effects on the GI system were excluded as were those unable to stop taking, for a period of 48 hours, any other medication that could possibly interfere with the results of measuring distension. All
Belts were fitted in the luteal phase (during days 18-20 of the menstrual cycle) in those individuals with regular periods. This was because of the results of a previous research which showed that there was a worsening in general well being at menses compared with the luteal phase (p<0.05) (191).

All patients have been asked to complete the validated IBS symptom severity questionnaire (203) detailing their symptoms including their distension and bloating scores.

Experimental design in Chapter Two, (section 2.4) explains recruitment methods (section 2.4.4), inclusion criteria (section 2.4.5) and exclusion criteria (section 2.4.6).

### 3.3.1 Ethical approval

South Manchester Research Committee approved the study and all participants gave written informed consent. REC reference number 03/SM/190, dated 19 April 2007.

### 3.3.2 Statistics

Comparisons of the various distension (girth) measures between subject groups were made using one-factor analyses of variance.
Subgroup analyses for the endometriosis group (comparing those ROME positive and ROME negative and comparing hypersensitives and normosensitives) were carried out using two-sample t-tests and no significant differences were found.

Pearson correlations were used to assess the relationship between pain threshold and distension measures, and Spearman correlations were used to assess the relationship between the subjective bloating score and the distension measures.

### 3.3.3 Abdominal inductance plethysmography

Abdominal inductance plethysmography works on the principle that a loop of wire forms an inductor, the inductance of which is dependent on the area enclosed by the loop (174, 179). The wire is sewn into a band of elasticated fabric (approximately 8.5 cm wide) in a zigzag fashion to allow for expansion (Respirtrace inductive sensor, Ambulatory Monitoring Inc., New York, USA) and is worn like a belt around the abdomen. Attached to the wire is a small electronic circuit unit, which incorporates an inductor in a resonant circuit whose output frequency varies with the area enclosed by the band and a data logger, which is a small battery operated microprocessor, records and stores the average frequency of the oscillator circuit for 30 seconds each minute. The data logger simultaneously records posture (standing, sitting and lying positions) via sealed mercury tilt switches (ASSE Mtech Europe Ltd., Essex, UK) taped to the subject’s chest and thigh. The cross sectional area of the abdomen recorded by the equipment is then converted into a circumferential measurement, as described previously.
The starting and ending time of each hour was recorded. The number of minutes the patients spent sitting down has also been recorded and the average abdominal girth for each of these hours was worked out using an auto programme which was run using an excel file. Although the lying time data has been ignored, the number of minutes for each hour lying down was collected and the abdominal girth average while the patients was lying down was also calculated using the same auto programme used in the neurogastroenterology unit. Figure 14 demonstrates how the belt is fitted on a patient. And an example of the output of the plethysmography belt is shown in Figure 15 for a normal individual and in Figure 16 for a person suffering distension.
Figure 14 Ambulatory abdominal inductance plethysmography (AIP) equipment.

The belt is fitted around the abdomen (B) and the Data Logger (DL) is attached to the belt. DL can be placed either on the right or left side of the patient according to their preferences. Two tilt switches are taped one to the side of the chest and one to the side of the thigh in order to record position as explained above (174, 179).
The figure above shows girth measurements in a healthy volunteer over 24 hours. As can be seen there is little difference between the baseline and the rest of the 24 hours. Three small peaks occurred, one in the morning, one early afternoon and one in the evening. These are likely to be after meals or snacks. Girth subsided further when the individual went to bed.
Figure 16 A distension graph for an IBS patient

The figure above is for a patient who was recruited for an earlier study. It represents an extreme condition of abdominal bloating and distension. Her abdominal girth was approximately 75 cm when she came fasting in the morning and it measured the same on the second morning. During the first day her abdominal girth was relatively stable until about 7 pm when it started to go up to a maximum level of 85 cm at 09.20 pm which is 10 cm more than the patient’s baseline. One hour later, girth subsided to 78 cm before having another small peak at about midnight. The patient went to bed at midnight and the distension started to decrease to 70 cm before increasing again in the morning to baseline level similar to the previous day. The data for standing and sitting are represented in red and blue respectively while the yellow colour represents lying down data.
3.3.4 Distension data analysis

We have included (20) IBS patients, (17) Minimal to mild endometriosis patients and (9) Moderate to severe endometriosis patients. The belt started to have some problems later and, therefore, we could not measure distension in other patients recruited for this study.

Only hourly readings with at least 30 minutes of standing/sitting data were included in the analysis and the outcomes were assessed as follows.

3.3.4.1 Average girth change from baseline

This is defined as the difference between the combined average girth over the first day and the second day (excluding the first hour of the second day) and the baseline girth (represented by that corresponding to the first hour of the second day).

3.3.4.2 Maximum girth

This is defined as the maximum increase in girth reached over the study period.

3.3.4.3 Area under the curve (AUC) change from baseline

This is defined as the difference between the AUC from the first hour of the first day to the last hour of the second day (excluding the first hour of the second day), standardised by the number of valid hours of measurement, and the baseline level (represented by that corresponding to the first hour of the second day).
In order to assess any relationship between IBS and endometriosis with respect to bloating and distension, the data were reanalysed by combining the endometriosis patients together (because they are rather a small number) and comparing them with IBS with respect to whether they are either ROME positive to IBS or viscerally hypersensitive. With respect to visceral hypersensitivity, this was looked at in respect to whether they were defined as hypersensitive using the 90% normal reference range used in Chapter Two (This was derived for the laparoscopic controls and found to be 31-48 mmHg).

### 3.4 RESULTS

Tables 2, 3, 4, 6 and 7 demonstrate the results for the average girth change from baseline, the maximum changing girth over the study period, the area under the curve for change curve, the bloating scores and the ROME positive patients within each of the distension groups respectively for all the groups of patients and controls studied. As can be seen, there were no significant differences between any of the groups in relation to abdominal girth measurement. Furthermore, when the data were further analysed looking at endometriosis patients in relation to visceral hypersensitivity, no significant changes emerged (Table 5).

With regard to bloating scores, it can be seen from Table 6, that the bloating scores in IBS patients were higher than in the endometriosis group as a whole, as well as when the endometriosis groups were divided into minimal-mild and moderate-severe.
All patients had to answer a question regarding whether they complain of bloating or not and to rate how severe their bloating is on a scale from 0 (no bloating) to 100 (very severe bloating).

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of subjects</th>
<th>Mean increase from baseline</th>
<th>(95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IBS</td>
<td>20</td>
<td>2.38</td>
<td>(0.75, 4.02)</td>
</tr>
<tr>
<td>All endo</td>
<td>26</td>
<td>2.64</td>
<td>(0.94, 4.35)</td>
</tr>
<tr>
<td>Min-Mild endo</td>
<td>17</td>
<td>3.31</td>
<td>(1.05, 5.56)</td>
</tr>
<tr>
<td>Mod-sev endo</td>
<td>9</td>
<td>1.39</td>
<td>(1.51, 4.30)</td>
</tr>
</tbody>
</table>

**Table 2 Average girth change from baseline:**

No significant difference between the groups of Minimal to Mild, Moderate to Severe endometriosis and the IBS groups (ANOVA; p=0.72), or between the groups (with endometriosis groups combined together; ANOVA; p=0.88)

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>IBS (n=20)</td>
<td>7.76</td>
<td>(4.95, 10.58)</td>
</tr>
<tr>
<td>All endo (n=26)</td>
<td>6.91</td>
<td>(4.65, 9.18)</td>
</tr>
<tr>
<td>Min-Mild endo (n=17)</td>
<td>7.11</td>
<td>(3.77, 10.46)</td>
</tr>
<tr>
<td>Mod-sev endo (n=9)</td>
<td>6.53</td>
<td>(3.73, 9.32)</td>
</tr>
</tbody>
</table>

**Table 3 Maximum girth over 24 hours**

No significant difference between the groups (ANOVA; p=0.76), or between the 4 groups, Minimal to Mild, Moderate to Severe endometriosis, laparoscopy healthy volunteers groups and the endometriosis groups combined together; ANOVA; p=0.71)
<table>
<thead>
<tr>
<th>Group</th>
<th>Number of subjects</th>
<th>Mean increase from baseline</th>
<th>(95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IBS</td>
<td>20</td>
<td>2.55</td>
<td>(0.87, 4.23)</td>
</tr>
<tr>
<td>All endo</td>
<td>26</td>
<td>2.68</td>
<td>(0.97, 4.40)</td>
</tr>
<tr>
<td>Min-Mild endo</td>
<td>17</td>
<td>3.35</td>
<td>(1.09, 5.62)</td>
</tr>
<tr>
<td>Mod-sev endo</td>
<td>9</td>
<td>1.42</td>
<td>(1.55, 4.39)</td>
</tr>
</tbody>
</table>

Table 4 Area under the curve (AUC) change from baseline

No significant difference between the groups (ANOVA; p=0.74), or between the 4 groups (with endometriosis groups combined; ANOVA; p=0.91).

<table>
<thead>
<tr>
<th>Endometriosis group as one group</th>
<th>Mean (SD)</th>
<th>P-value (t-test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Max distension over 2 days</td>
<td>Hypersensitive (n=17)</td>
<td>Normosensitive (n=9)</td>
</tr>
<tr>
<td></td>
<td>7.75 (6.6)</td>
<td>5.33 (2.52)</td>
</tr>
<tr>
<td>AUC (over 1st day) change from baseline</td>
<td>3.88 (4.74)</td>
<td>1.25 (3.65)</td>
</tr>
<tr>
<td>AUC (over 2 days) change from baseline</td>
<td>3.44 (4.62)</td>
<td>1.25 (3.21)</td>
</tr>
</tbody>
</table>

Table 5 Distension in Hyper and Normosensitive endometriosis patients

Although the hyper sensitive endometriosis patients seemed to have distended more, no statistically significant differences between the hypersensitive and normosensitive endometriosis patients were found.
### Table 6 Bloating scores in all groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of subjects</th>
<th>Bloating score (mean range)</th>
<th>(95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IBS *</td>
<td>20</td>
<td>69.00 (25.00-100)</td>
<td>(30.81, 56.83)</td>
<td></td>
</tr>
<tr>
<td>All endo</td>
<td>26</td>
<td>43.18 (00.00-100.00)</td>
<td>(34.44, 51.93)</td>
<td>P=&lt; 0.05 with IBS</td>
</tr>
<tr>
<td>Min-Mild endo</td>
<td>17</td>
<td>43.82 (00.00-100.00)</td>
<td>(30.31, 53.88)</td>
<td>P=&lt; 0.05 with IBS</td>
</tr>
<tr>
<td>Mod-sev endo</td>
<td>9</td>
<td>42.10 (22.00-75.00)</td>
<td>(52.24, 85.75)</td>
<td>P=&lt; 0.05 with IBS</td>
</tr>
</tbody>
</table>

IBS patients exhibit significantly more bloating than the other groups.

### Table 7 ROME criterion in the distension data

<table>
<thead>
<tr>
<th>Group</th>
<th>No. (%) ROME positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>IBS (n=20)</td>
<td>20 (100%)</td>
</tr>
<tr>
<td>All endo (n=26)</td>
<td>18 (69%)</td>
</tr>
<tr>
<td>Min-Mild endo (n=17)</td>
<td>13 (76%)</td>
</tr>
<tr>
<td>Mod-sev endo (n=9)</td>
<td>5 (56%)</td>
</tr>
</tbody>
</table>

As can be seen from Table 7, more than 50% of patients with moderate to severe endometriosis whose distension was recorded had symptoms matching the Rome criteria for IBS. Nearly three quarters of minimal to mild endometriosis patients and all IBS patients who had distension measured had symptoms suggestive of IBS.
3.5 DISCUSSION

These results suggest that there is little difference between patients with IBS and endometriosis with respect to distension. However, it has to be emphasised that the endometriosis group was rather small because of technical difficulties with the equipment as well as the fact that these patients were reluctant to come for further studies when the belt failed.

Despite these confounding factors, it is perhaps not surprising that little in the way of differences were found between the IBS and endometriosis groups. As can be seen from Chapter Two (2.6), visceral sensitivity was equally common in patients with IBS and endometriosis and, as will become clear from Chapter 3, the proportion of patients fulfilling ROME III for IBS, in the endometriosis group was also very high. Consequently, the various pathophysiological mechanisms involved in IBS, Visceral sensitivity, bloating and distension might be strongly represented in both groups.

Bloating is an extremely intrusive symptom to which a considerable amount of attention has been placed in IBS patients. It also occurs very commonly in endometriosis, although it hasn’t been studied in this condition. Patients with IBS often rank bloating as their most disturbing symptom and it is a very difficult condition to treat. However, now that the various pathophysiological mechanisms involved in bloating and distension are beginning to be understood, more logical
approaches to treatment should be possible. For instance, it might be worthwhile considering targeting VS with drugs such as tricyclic antidepressants or Alpha 2 delta ($\alpha_2\delta$) ligands, Gabapentin and Pregabalin (97). Bloating in the IBS group was significantly higher than the endometriosis group and this may be because more patients in the IBS group than in the endometriosis group were hypersensitive Chapter Two, (section 2.6). Alternatively, it could be that IBS patients are more aware of the symptoms whereas patients with endometriosis who were not diagnosed with IBS, might have related the sensation of bloating to their gynaecological system and a sensation of pressure in their pelvis. On the other hand, it could be that because fewer of the endometriosis groups had IBS symptoms than the IBS group, bloating is more common and more severe in IBS patients.

Similarly, it is well known in patients with IBS that a high fibre diet makes their bloating worse although the mechanism for this observation is unclear. It might be that insoluble fibre in particular, leads to increased visceral sensitivity, Consequently, advising a reduction in fibre intake, particularly in the insoluble variety is worth considering. Where constipation and slow transit are involved in this problem, then speeding up transit or relieving constipation is also a worthwhile approach. As discussed in Chapter one, the role of microbiota in IBS is also an area of intense research at present. However, it is not yet known whether an abnormal bacterial flora is related to visceral sensitivity but there is some emerging
evidence that the use of probiotics can enhance transit and reduce distension (88) and also have positive effects on symptomatic bloating (204).

In conclusion, this rather preliminary study does show that the levels of bloating and distension are similar to those found in IBS and suggests that they both cause a problem in endometriosis. Therefore, using the approaches to try to treat this condition that are used in IBS is well worth considering especially as they are not associated with any significant risk or side effects. In addition, taking a careful history around bowel habits and symptoms especially those suggestive of visceral hypersensitivity, such as rectal dissatisfaction, may help in the choice of which treatment to choose.
CHAPTER FOUR: ABDOMINAL SYMPTOMS AND QUALITY OF LIFE IN PATIENTS WITH IRRITABLE BOWEL SYNDROME AND ENDOMETRIOSIS
4.1 INTRODUCTION

Previous studies have shown that up to 50% of patients referred to gynaecological clinics with abdominal pain are suffering from IBS (5) and often have a poor outcome sometimes associated with surgical intervention. There is currently no diagnostic test for Irritable Bowel Syndrome (IBS) and the diagnosis is principally based on symptomatology (39). These patients also often have poor quality of life.

In women with IBS who happen to have a gynaecological symptom such as heavy periods, their abdominal pain can be wrongly ascribed to a gynaecological cause and they may be referred to gynaecological clinics. Endometriosis is characterised clinically by pelvic pain and altered menstruation and in recent years, laparoscopy has been widely adopted as a relatively early investigation in the assessment of abdominal and pelvic pain in the gynaecological setting. If endometriosis is detected, however mild, the pain is often attributed to this condition and treated as such. However, if visceral hypersensitivity or IBS are contributing to these problems, different treatment approaches might be worth considering.

4.2 AIM OF RESEARCH

The aim of this study was to compare abdominal symptoms and quality of life in patients with irritable bowel syndrome and endometriosis and to see if any differences could be of clinical value.
4.3 OBJECTIVES

1. To determinate the percentage of patients with endometriosis who fulfil the ROME III criteria for IBS.

2. To compare gastrointestinal and gynaecological symptoms in IBS and endometriosis and compare them to the healthy volunteer group.

3. To look at the differences in quality of life among various groups.

4. To compare gastrointestinal and gynaecological symptoms and quality in life among ROME positive and ROME negative endometriosis patients.

5. To compare gastrointestinal and gynaecological symptoms and quality in life in patients with or without visceral hypersensitivity.

4.4 METHODS

As discussed in Chapter two, twenty women with minimal to mild endometriosis, 20 with moderate to severe endometriosis, 20 with laparoscopy negative abdominal pain, 20 asymptomatic female controls undergoing laparoscopic sterilisation and 20 women with IBS were recruited and completed validated questionnaires detailing all their symptoms, in addition to quality of life questionnaire.

All subjects completed the following questionnaires: a ROME III diagnostic questionnaire (73), IBS symptom severity questionnaire (203) and quality of life
questionnaire. Gynaecological symptoms and other medical and family history were also recorded.

4.5 RESULTS

Figure 17 shows the distribution of patients in the various groups fulfilling ROME III criteria for irritable bowel symptoms. The actual values for these data are given in Table 8 as well as the distribution of the various subtypes of irritable bowel syndrome, that is diarrhoea predominant, constipation predominant, mixed and unspecified IBS. As we anticipated a 100% of IBS fulfilled the ROME III criteria as well as 85% of the laparoscopy negative abdominal pain, furthermore approximately two thirds of endometriosis patients had symptoms consistent with IBS. Figure 18 shows the symptom severity scores for these patients and, as can be seen, the endometriosis patients scored highly although not as quite as highly as laparoscopy negative abdominal pain patients, with the IBS patients achieving the highest scores. The actual values for the individual component of the IBS symptoms severity score are given in Table 9, where the patients of endometriosis were broken down to those fulfilling or not fulfilling the ROME III for IBS. As can be seen those having symptoms consistent with IBS, had highly significantly greater scores for pain, interference with life with the bloating score being higher in the ROME III but not reaching significance.

Table 10 documents the gynaecological symptoms in patients with IBS and endometriosis with the latter again broken down to those fulfilling or not fulfilling the
ROME III criteria for IBS. As can be seen, there was no significant difference in any of these items between endometriosis patients who did or did not meet the ROME II criteria for IBS. However the endometriosis groups as a whole did appear to suffer from more frequent pain with intercourse than those with IBS and its’ severity was worse than those with IBS. Similarly, period pain and its severity were worse the most in endometriosis as a whole compared with those with IBS.

Table 11 documents the visceral hypersensitivity that was reported in Chapter two in patients with endometriosis and IBS but divides the patients with endometriosis into those who fulfil the ROME criteria for IBS and those who don’t. As might be anticipated, the ROME positive individuals show greater sensitivity for first sensation, stool sensation and pain than those who do not fulfil the ROME criteria, although this does not reach significance. It is also noteworthy that the sensory thresholds in the ROME positive endometriosis group are very similar to those observed in IBS.

Patients with endometriosis were also divided into hypersensitive and normosensitive using the 90% reference range for sensitivity 31-48 mmHg used in Chapter two and compared with the IBS group. Table 12 shows the visceral sensitivity readings for these three groups. As expected, the viscerally hypersensitive endometriosis individuals showed greater sensitivity for first sensation, pain sensation and stool than those who were defined as normosensitive using the reference range above. The differences were significant.
between both groups with regard to pain pressure threshold and stool pressure threshold. It is also worth mentioning that the sensory thresholds in the hyper sensitive endometriosis subjects were very similar to those seen in the IBS group.

With regard to the quality of life results, Table 13, documents the quality of life items and compares the scores of the endometriosis group as a whole and the IBS group with healthy volunteers. As can be seen, both endometriosis and IBS significantly and adversely affect quality of life. Table 14, compares IBS and endometriosis in terms of the same QOL items and as can be seen there is little difference between the two groups. Table 15 breaks down the endometriosis group into ROME positive and ROME negative patients. As can be seen, quality of life scores again were very similar between the two groups of patients.
4.5.1 GI and other symptoms results

![Rome Positive Graph](image)

Figure 17 ROME III positives.

All IBS patients, 85% of laparoscopy negative abdominal pain patients, 65% of minimal to mild endometriosis patients and more than 50% of moderate to severe endometriosis patients fulfilled Rome III criteria for IBS.
The table above documents the number of patients fulfilling the Rome III criteria for irritable bowel syndrome in each study group. In addition, patients are divided into diarrhoea, constipation, mixed or unclassified bowel sub-groups.

<table>
<thead>
<tr>
<th></th>
<th>HV (20)</th>
<th>Min-Mild (20)</th>
<th>Mod-Severe (20)</th>
<th>Lap- Neg (20)</th>
<th>IBS 20</th>
</tr>
</thead>
<tbody>
<tr>
<td>ROME positive n, (%)</td>
<td>0 (0%)</td>
<td>13* (65%)</td>
<td>11* (55%)</td>
<td>17* (85%)</td>
<td>20* (100%)</td>
</tr>
<tr>
<td>IBS-D (n)</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>IBS-C (n)</td>
<td>0</td>
<td>6</td>
<td>4</td>
<td>11</td>
<td>16</td>
</tr>
<tr>
<td>IBS-Mixed (n)</td>
<td>0</td>
<td>4</td>
<td>1</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>IBS-U (n)</td>
<td>0</td>
<td>2</td>
<td>5</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

* comparison with controls: p<0.001
Figure 18 IBS severity scores

The figure above shows the IBS symptom severity scores in the various groups studied. As can be seen, controls all fell below the threshold for symptom severity whereas IBS patients exhibited the highest scores.
<table>
<thead>
<tr>
<th>IBS Symptoms Severity Score</th>
<th>ENDO-ROME + (Mean-Range)</th>
<th>ENDO-ROME - (Mean-Range)</th>
<th>All Endo (Mean-Range)</th>
<th>IBS (Mean-Range)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abd Pain Sev</td>
<td>52.12 (42.42 61.83)</td>
<td>18.06(1.75 34.37)</td>
<td>38.50(28.60 48.40)</td>
<td>55.20(43.54 66.86)</td>
<td>0.000</td>
</tr>
<tr>
<td>Bloating Sev</td>
<td>43.95(32.64 55.28)</td>
<td>31.37(20.42 42.33)</td>
<td>38.92(30.93 46.92)</td>
<td>72.05(61.22 82.88)</td>
<td>0.12</td>
</tr>
<tr>
<td>Pain interference with life</td>
<td>58.28(48.97 67.61)</td>
<td>41.46(29.98 52.94)</td>
<td>51.85(44.42 59.29)</td>
<td>63.94(49.73 78.14)</td>
<td>0.014</td>
</tr>
<tr>
<td>BH dissatisfaction</td>
<td>63.54(52.16 74.92)</td>
<td>34.56(20.48 48.64)</td>
<td>51.95(42.34 61.56)</td>
<td>79.55(68.89 90.21)</td>
<td>0.002</td>
</tr>
<tr>
<td>IBS SQ score</td>
<td>279.41(246.33 312.50)</td>
<td>133.12(82.55 183.70)</td>
<td>220.90(185.35 256.45)</td>
<td>340(299.88 380.12)</td>
<td>.000</td>
</tr>
</tbody>
</table>

Table 9 IBS Symptoms Severity Score

In this table, patients with endometriosis were broken down into ROME positive and ROME negative patients. The table shows that those having symptoms consistent with IBS, had highly significantly greater scores for pain and interference with life. Bloating scores were higher in the ROME III positive individuals but the differences did not reach significance.
Table 10 Gynaecological symptoms

A comparison of gynaecological symptoms in the different group studied. The data are presented as number, mean range or percentage according to the question. As can be seen, there were no significant difference in any of these items between endometriosis patients who did or did not meet the ROME II criteria for IBS. However patients in the endometriosis groups as a whole had more frequent pain with intercourse and the severity was worse than those with IBS. The same pattern was observed in relation to menstruation.
Table 11 Visceral sensitivity in endometriosis ROME positive, ROME negative, all and IBS.

This table shows a comparison of visceral sensitivity readings between patients with endometriosis who fulfilled the criteria for IBS and those who did not. Patients who fulfilled the diagnostic criteria for IBS were more viscerally sensitive than those who did not and the pressure readings were very similar to those in the IBS group.
Table 12 Visceral sensitivity in hypersensitive, normosensitive endometriosis and IBS groups

This table summarises the barostat results in the IBS and endometriosis groups dividing the latter into normosensitive and hypersensitive groups. Hypersensitive endometriosis patients’ sensitivity thresholds were similar to the thresholds seen in IBS.
4.5.2 Quality of life results

![Quality of life scores](image)

**Figure 19 Quality of life scores.**

The figure above shows the total score for quality of life for each group. No significant differences between groups were found.
<table>
<thead>
<tr>
<th>Quality of Life</th>
<th>Healthy volunteer Mean 95%CI</th>
<th>All Endo Mean 95%CI</th>
<th>P value/T-test Healthy/ENDO</th>
<th>IBS Mean 95%CI</th>
<th>P value/ T-test Healthy/IBS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total score Quality of Life</td>
<td>400.59(377.88 423.29)</td>
<td>334.68(304.60 364.76)</td>
<td>0.052</td>
<td>318.75(256.54 380.96)</td>
<td>0.056</td>
</tr>
<tr>
<td>Coping with problem?</td>
<td>87.00(79.51 94.49)</td>
<td>63.15(55.08 71.21)</td>
<td>0.000</td>
<td>51.64(37.78 65.51)</td>
<td>0.000</td>
</tr>
<tr>
<td>Feeling confident and secure</td>
<td>87.57(82.79 92.36)</td>
<td>69.37(63.27 75.47)</td>
<td>0.000</td>
<td>49.64(34.54 64.75)</td>
<td>0.000</td>
</tr>
<tr>
<td>How well are you sleeping?</td>
<td>78.79(67.98 89.59)</td>
<td>66.25(59.58 72.86)</td>
<td>0.110</td>
<td>57.52(44.78 70.27)</td>
<td>0.030</td>
</tr>
<tr>
<td>How often are you irritable</td>
<td>61.36(51.18 71.55)</td>
<td>48.10(40.21 55.95)</td>
<td>0.048</td>
<td>48.76(35.97 61.55)</td>
<td>0.109</td>
</tr>
<tr>
<td>How often do you worry?</td>
<td>58.42(49.05 67.78)</td>
<td>48.70(40.19 57.20)</td>
<td>0.161</td>
<td>47.06(30.59 63.52)</td>
<td>0.216</td>
</tr>
<tr>
<td>How much are you able enjoy life?</td>
<td>83.68(75.72 91.64)</td>
<td>69.37(63.14 75.60)</td>
<td>0.008</td>
<td>63.23(47.82 78.65)</td>
<td>0.02</td>
</tr>
<tr>
<td>Feeling of hopefulness?</td>
<td>84.94(74.06 95.83)</td>
<td>68.42(61.35 75.50)</td>
<td>0.010</td>
<td>49.64(32.62 66.67)</td>
<td>0.001</td>
</tr>
<tr>
<td>How well do you feel Physically?</td>
<td>82.16(73.00 91.31)</td>
<td>56.72(49.51 63.93)</td>
<td>0.000</td>
<td>54.76(40.75 68.78)</td>
<td>0.001</td>
</tr>
<tr>
<td>Relationship with others?</td>
<td>84.47(77.24 91.70)</td>
<td>79.97(75.22 84.72)</td>
<td>0.201</td>
<td>66.94(51.15 82.73)</td>
<td>0.035</td>
</tr>
<tr>
<td>Ability to maintain friendship?</td>
<td>92.05(85.80 98.29)</td>
<td>80.90(74.44 87.35)</td>
<td>0.023</td>
<td>80.52(69.58 91.47)</td>
<td>0.061</td>
</tr>
<tr>
<td>Feeling of inferiority</td>
<td>75.42(64.16 86.67)</td>
<td>70.55(63.17 77.92)</td>
<td>0.453</td>
<td>66.76(51.44 82.08)</td>
<td>0.224</td>
</tr>
<tr>
<td>Feeling wanted</td>
<td>83.84(76.50 91.17)</td>
<td>70.20(61.00 79.39)</td>
<td>0.021</td>
<td>66.29(49.03 83.55)</td>
<td>0.031</td>
</tr>
<tr>
<td>Feeling helpless and not in control of your life</td>
<td>77.78(70.61 84.96)</td>
<td>64.42(56.56 72.51)</td>
<td>0.014</td>
<td>54.94(41.02 68.85)</td>
<td>0.003</td>
</tr>
<tr>
<td>How much difficult do you have making decision?</td>
<td>84.15(75.94 92.37)</td>
<td>64.00(17.71 82.12)</td>
<td>0.001</td>
<td>48.70(33.54 63.87)</td>
<td>0.001</td>
</tr>
<tr>
<td>Enjoyment of leisure time?</td>
<td>79.94(71.93 87.95)</td>
<td>70.62(63.38 77.86)</td>
<td>0.115</td>
<td>64.82(48.91 80.72)</td>
<td>0.082</td>
</tr>
</tbody>
</table>
Table 13 Quality of life in healthy volunteers, IBS and the endometriosis group as a whole.

This table breaks the quality of life into its major domains, comparing healthy volunteers, the endometriosis group as a whole group and patients with IBS.
<table>
<thead>
<tr>
<th>Quality of Life</th>
<th>IBS Mean 95%CI</th>
<th>All Endo Mean 95%CI</th>
<th>P value/ T-test IBS /ENDO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total score Quality of Life</td>
<td>318.75(256.54 380.96)</td>
<td>334.68(304.60 364.76)</td>
<td>0.585</td>
</tr>
<tr>
<td>Coping with problem?</td>
<td>51.64(37.78 65.51)</td>
<td>63.15(55.08 71.21)</td>
<td>0.128</td>
</tr>
<tr>
<td>Feeling confident and secure</td>
<td>49.64(34.54 64.75)</td>
<td>69.37(63.27 75.47)</td>
<td>0.004</td>
</tr>
<tr>
<td>How well are you sleeping?</td>
<td>57.52(44.78 70.27)</td>
<td>66.25(59.58 72.86)</td>
<td>0.178</td>
</tr>
<tr>
<td>How often are you irritable</td>
<td>48.76(35.97 61.55)</td>
<td>48.10(40.21 55.95)</td>
<td>0.926</td>
</tr>
<tr>
<td>How often do you worry?</td>
<td>47.06(30.59 63.52)</td>
<td>48.70(40.19 57.20)</td>
<td>0.842</td>
</tr>
<tr>
<td>How much are you able enjoy life?</td>
<td>63.23(47.82 78.65)</td>
<td>69.37(63.14 75.60)</td>
<td>0.445</td>
</tr>
<tr>
<td>Feeling of hopefulness?</td>
<td>49.64(32.62 66.67)</td>
<td>68.42(61.35 75.50)</td>
<td>0.043</td>
</tr>
<tr>
<td>How well do you feel Physically?</td>
<td>54.76(40.75 68.78)</td>
<td>56.72(49.51 63.93)</td>
<td>0.779</td>
</tr>
<tr>
<td>Relationship with others?</td>
<td>66.94(51.15 82.73)</td>
<td>79.97(75.22 84.72)</td>
<td>0.111</td>
</tr>
<tr>
<td>Ability to maintain friendship?</td>
<td>80.52(69.58 91.47)</td>
<td>80.90(74.44 87.35)</td>
<td>0.903</td>
</tr>
<tr>
<td>Feeling of inferiority</td>
<td>66.76(51.44 82.08)</td>
<td>70.55(63.17 77.92)</td>
<td>0.453</td>
</tr>
<tr>
<td>Feeling wanted</td>
<td>66.29(49.03 83.55)</td>
<td>70.20(61.00 79.39)</td>
<td>0.395</td>
</tr>
<tr>
<td>Feeling helpless and not in control of your life</td>
<td>54.94(41.02 68.85)</td>
<td>64.42(56.56 72.51)</td>
<td>0.171</td>
</tr>
<tr>
<td>How much difficult do you have making decision?</td>
<td>48.70(33.54 63.87)</td>
<td>64.00(17 71.82)</td>
<td>0.106</td>
</tr>
<tr>
<td>Enjoyment of leisure time?</td>
<td>64.82(48.91 80.72)</td>
<td>70.62(63.38 77.86)</td>
<td>0.466</td>
</tr>
</tbody>
</table>

Table 14 Quality of life in IBS and all endometriosis patients grouped together.
<table>
<thead>
<tr>
<th>Quality of Life</th>
<th>END-ROME + Mean 95%CI</th>
<th>END-ROME – Mean 95%CI</th>
<th>AllEndo Mean 95%CI</th>
<th>IBS Mean 95%CI</th>
<th>P value / T-test ENDOROME +/-</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total score</td>
<td>349.52(306.55 292.49)</td>
<td>312.44(270.34 354.053)</td>
<td>334.68(304.60 364.76)</td>
<td>318.75(256.54 380.96)</td>
<td>0.226</td>
</tr>
<tr>
<td>Coping with problem?</td>
<td>65.50(56.27 74.72)</td>
<td>59.63(43.66 75.59)</td>
<td>63.15(55.08 71.21)</td>
<td>51.64(37.78 65.51)</td>
<td>0.477</td>
</tr>
<tr>
<td>Feeling confident and secure</td>
<td>67.96(60.55 73.37)</td>
<td>71.50(60.00 82.99)</td>
<td>69.37(63.27 75.47)</td>
<td>49.64(34.54 64.75)</td>
<td>0.572</td>
</tr>
<tr>
<td>How well are you sleeping?</td>
<td>62.62(53.44 71.81)</td>
<td>71.62(61.73 81.51)</td>
<td>66.25(59.58 72.86)</td>
<td>57.52(44.78 70.27)</td>
<td>0.183</td>
</tr>
<tr>
<td>How often are you irritable</td>
<td>46.25(35.50 56.99)</td>
<td>50.87(38.10 63.64)</td>
<td>48.10(40.21 55.95)</td>
<td>48.76(35.97 61.55)</td>
<td>0.568</td>
</tr>
<tr>
<td>How often do you worry?</td>
<td>53.67(43.31 64.02)</td>
<td>41.25(26.00 56.49)</td>
<td>48.70(40.19 57.20)</td>
<td>47.06(30.59 63.52)</td>
<td>0.15</td>
</tr>
<tr>
<td>How much are you able to enjoy life?</td>
<td>70.50(63.58 77.41)</td>
<td>67.69(54.94 80.43)</td>
<td>69.37(63.14 75.60)</td>
<td>63.23(47.82 78.65)</td>
<td>0.661</td>
</tr>
<tr>
<td>Feeling of hopefulness?</td>
<td>70.33(61.31 79.35)</td>
<td>65.56(52.96 78.15)</td>
<td>68.42(61.35 75.50)</td>
<td>49.64(32.62 66.67)</td>
<td>0.511</td>
</tr>
<tr>
<td>How well do you feel physically?</td>
<td>54.33(45.56 63.11)</td>
<td>60.31(46.86 73.76)</td>
<td>56.72(49.51 63.93)</td>
<td>54.76(40.75 68.78)</td>
<td>0.418</td>
</tr>
<tr>
<td>Relationship with others?</td>
<td>82.54(76.08 89.00)</td>
<td>76.12(68.80 83.44)</td>
<td>79.97(75.22 84.72)</td>
<td>66.94(51.15 82.73)</td>
<td>0.184</td>
</tr>
<tr>
<td>Ability to maintain friendship?</td>
<td>86.25(80.14 92.35)</td>
<td>72.87(59.57 86.17)</td>
<td>80.90(74.44 87.35)</td>
<td>80.52(69.58 91.47)</td>
<td>0.038</td>
</tr>
<tr>
<td>Feeling of inferiority</td>
<td>71.37(61.06 81.68)</td>
<td>69.31(57.83 80.79)</td>
<td>70.55(63.17 77.92)</td>
<td>66.76(51.44 82.08)</td>
<td>0.786</td>
</tr>
<tr>
<td>Feeling wanted</td>
<td>77.12(66.36 87.88)</td>
<td>59.81(43.28 76.34)</td>
<td>70.20(61.00 79.39)</td>
<td>66.29(49.03 83.55)</td>
<td>0.061</td>
</tr>
<tr>
<td>Feeling helpless and not in control of your life</td>
<td>70.54(62.13 78.95)</td>
<td>55.25(39.21 71.28)</td>
<td>64.42(56.56 72.51)</td>
<td>54.94(41.02 68.85)</td>
<td>0.060</td>
</tr>
<tr>
<td>How much difficult do you have making decision?</td>
<td>68.37(59.13 77.61)</td>
<td>57.43(42.87 71.99)</td>
<td>64.00(47.17 71.82)</td>
<td>48.70(33.54 63.87)</td>
<td>0.169</td>
</tr>
<tr>
<td>Enjoyment of leisure time?</td>
<td>76.62(69.03 84.21)</td>
<td>61.62(47.58 75.66)</td>
<td>70.62(63.38 77.86)</td>
<td>64.82(48.91 80.72)</td>
<td>0.058</td>
</tr>
</tbody>
</table>
Table 15 Quality of life in different groups studied

The table above compares quality of life between the ROME positive endometriosis group, the ROME negative endometriosis group, the endometriosis group as a whole group and the IBS patients.
4.6 DISCUSSION

These results show that symptoms suggestive of irritable bowel syndrome are extremely common in the group of gynaecological patients. It’s perhaps not surprising that the higher level of ROME positive patients was in the laparoscopically negative abdominal pain group. This suggests that this group largely consists of patients with IBS and this conclusion is also supported by the findings from (Chapter Two) that these patients are also viscerally hypersensitive. This suggests that particular attention should be paid to gastrointestinal symptoms in patients presenting to the gynaecologist with abdominal pain in whom laparoscopy is negative. If, as a result of this there is a strong suggestion that these patients may have a gastrointestinal component to their pain, it may be advisable to treat the gastrointestinal aspects before going on to further investigation.

Nearly two thirds of endometriosis patients also met the symptom criteria for IBS. It was interesting to note that the moderate to severe endometriosis patients had a slightly lower prevalence of IBS symptoms than the minimal to mild groups which gives an indication that the problem of IBS maybe more important in the minimal to mild endometriosis group than the moderate to severe group, although this difference did not reach significant. This makes sense as it would seem likely that the more severe endometriosis is, the more likely it is to cause symptoms as a
result of the endometriosis itself rather than other confounding symptoms from coexisting IBS. Furthermore, the IBS symptom severity data support these conclusions.

When endometriosis patients are divided into ROME positive and ROME negative individuals, (Table 9), then the ROME positive patients behave very similarly to the IBS patients with respect to their abdominal pain. In contrast, the ROME negative patients have significantly less pain in terms of severity which suggests that the IBS is driving symptomatology to some extent irrespective of the severity of the extensiveness of the endometriosis. It does seem reasonable to assume that the abdominal pain rating in the IBS symptoms severity score is likely to be capturing both IBS pain and endometriosis pain although this cannot be proved conclusively. In contrast the gynaecological symptoms recorded in Table 10 do appear to be more prominent in the endometriosis groups and as a whole when compared with the IBS group. The problem with the interpretation of these results is that when they are further broken down to subgroups, the numbers become rather small for meaningful interpretation.

With respect to quality of life, it can be seen from Tables 13, 14, 15, and Figure 19 that the endometriosis group is behaving in a similar manner to those with IBS. It is a little difficult to decide whether the endometriosis or the IBS is adversely affecting the quality of life, although the finding in table 15 suggests that it could be the IBS symptoms in the ROME positive group and the endometriosis in the ROME
negative group. It seems to be reasonable that both conditions can affect quality of life especially, in the case of endometriosis, when it is sufficiently extensive. This is supported by Figure 19 which shows quality of life is equally affected in minimal to mild and moderate to severe patients with endometriosis.

The interpretation of the data on symptoms severity and quality of life in IBS and endometriosis is difficult although it is clear that the degree of suffering in these patients is rather high. Rather than trying to over interpret the data, it may be safer to conclude that this chapter highlights the challenges associated with IBS and endometriosis rather than necessarily offering an explanation about what exactly is going on.
CHAPTER FIVE: A COMPARISON OF THE DEMOGRAPHY, MOOD AND NONCOLONIC SYMPTOMATOLOGY IN PATIENTS WITH IRRITABLE BOWEL SYNDROME AND ENDOMETRIOSIS
5.1 INTRODUCTION

It is well known that patients with IBS suffer from a series of non-colonic symptoms such as low backache, lethargy, nausea and urinary symptoms suggestive of an irritable bladder (1). These features are important as they add to the symptom burden of IBS patients and reduce quality of life. In addition, they lead to these patients being subjected to a variety of investigations and treatments which may not necessarily be in their best interest. A previous study comparing patients with IBS and inflammatory bowel disease has shown that the presence of these non-colonic symptoms have diagnostic value because their presence indicates that the diagnosis is more likely to be IBS especially when the inflammatory bowel disease is in remission (205).

If the presence of noncolonic symptoms had a diagnostic value in separating IBS from inflammatory bowel disease, it was wondered whether noncolonic symptoms might be helpful in distinguishing IBS from endometriosis. In addition, it was thought that they might be more common in endometriosis patients who have IBS or visceral hypersensitivity. If this is the case, then it might be possible that enquiring about these symptoms could help a decision to be made about whether these symptoms, if present in an endometriosis patient, are being contributed to by their IBS or visceral hypersensitivity.
In addition, it was felt that it would be worth recording mood at the same time to see if this had any influence on symptomatology.

5.2 AIM OF RESEARCH

The aim of this research is to compare demography, mood and noncolonic symptomatology in patients with irritable bowel syndrome and endometriosis.

5.2.1 Ethical approval

South Manchester Research Committee has approved the study and all participants gave written informed consent. REC reference number 03/SM/190, date 19 April 2007.

5.3 METHODS

One hundred patients have been included in this study and they were divided into 5 groups of 20 patients each. These were laparoscopic sterilisation, healthy volunteers (HV), minimal to mild endometriosis (Min-Mild.), moderate to severe endometriosis (Mod-Sev), laparoscopy negative abdominal pain (Lap-Neg) and subjects with IBS (IBS) and were recruited from the outpatient department of the University Hospital of South Manchester NHS Foundation Trust. All subjects underwent appropriate investigations to rule out organic gastrointestinal disease and did not exhibit a functional disorder of the upper gastrointestinal tract that was more prominent than their IBS Symptomatology. All subjects drank below the
recommended limit of alcohol and were not taking medications that might affect gastrointestinal function for at least 48 hours prior to taking part in the study.

In addition to the usual demographic questions that are documented in Table 16, patients were also asked to complete noncolonic symptoms questionnaires, and the hospital anxiety depression questionnaire (1, 206). The noncolonic symptoms questionnaire consists of 15 items which are scored on a 0 to 100 point scale which enables each item to be scored as well as a total score to be derived (1). The hospital anxiety depression questionnaire (HAD) consists of 7 anxiety related and 7 depression related questions which can be scored between 0 and 3 giving a maximum score of 21 for either anxiety or depression. A score of 10 or above is usually regarded as indicating significant anxiety or depression (Appendix 2).

5.4 RESULTS

Table 16 documents the demographic data for all the patients assessed in this study. As can be seen, they are very similar in terms of age, ethnic background, height and parity. There were significant differences with respect to weight and alcohol consumption. With regard to weight, the moderate to severe endometriosis patients were significantly heavier than controls, whereas the weight of IBS patients was significantly lower than controls. Similarly alcohol consumption was significantly higher in moderate to severe endometriosis patients, and alcohol intake was significantly less in the IBS group. There were also some minor
significant differences with regard to smoking, with non smokers being particularly prominent in the IBS group.

Table 17 documents all the symptoms that are included in the noncolonic symptomatology questionnaire and compares their prevalence in healthy volunteers with all the endometriosis patients and all the IBS patients. As can be seen, the endometriosis group behave very similarly to the IBS group in terms of a significant increase.

Table 18 breaks the endometriosis patients down into ROME positive and ROME negative individuals and, as can be seen, there is no significant difference between these groups. The ROME positive endometriosis patients behave in a way similar to the IBS patients more than the ROME negative individuals.

Figure 20 shows the results for HAD anxiety score for all 5 groups. As can be seen, all four patient groups are significantly more anxious than the controls and there is little difference between the patient groups. None of the patient groups exceeded the cut off of 10 that would have indicated significant anxiety.

Figure 21 details the results for HAD depression scores for the different groups. As can be seen there is a little more scatter than for anxiety but none of the differences reaches significance. Furthermore, the depression scores are all very low with none of the patient groups even getting near the score which would indicate significant depression.
5.4.1 Demographic results

The following data are expressed as means and ranges of numbers for laparoscopic sterilisation healthy volunteers (Lap HV), minimal to mild endometriosis (Min-Mild), moderate to severe endometriosis (Mod-Severe), laparoscopy negative abdominal pain (Lap-Neg), subjects with IBS (IBS).
The table shows that patients in all groups were similar in terms of age, ethnic background, height and parity. There were significant differences with respect to weight and alcohol consumption with moderate to severe endometriosis patients being significantly heavier than controls. In contrast, the weight of IBS patients was significantly lower than controls. Furthermore, moderate to severe endometriosis patients had significantly higher levels of alcohol consumption, while the IBS group had significantly lower alcohol intake than controls. Non smokers were also prominent in the IBS group.
<table>
<thead>
<tr>
<th>NONCOLONIC</th>
<th>ENDO-ROME + (Mean-Range)</th>
<th>ENDO-ROME- (Mean-Range)</th>
<th>All Endo (Mean-Range)</th>
<th>IBS (Mean-Range)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>26.12(16.40 35.85)</td>
<td>14.50(6.28 22.72)</td>
<td>20.83(13.18 28.49)</td>
<td>29.37(13.50 45.24)</td>
<td>0.085</td>
</tr>
<tr>
<td>Difficulties</td>
<td>33.54 (20.48 46.60)</td>
<td>21.81(5.12 38.50)</td>
<td>25.34(14.86 35.84)</td>
<td>35.31(18.30 52.32)</td>
<td>0.250</td>
</tr>
<tr>
<td>Finishing meals</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>46.87(36.03 57.72)</td>
<td>44.00(30.29 57.71)</td>
<td>46.13(36.08 56.18)</td>
<td>44.62(30.48 58.77)</td>
<td>0.731</td>
</tr>
<tr>
<td>Backache</td>
<td>53.95(43.07 64.85)</td>
<td>43.81(25.78 61.85)</td>
<td>47.74(37.03 58.45)</td>
<td>58.25(40.07 76.43)</td>
<td>0.289</td>
</tr>
<tr>
<td>Lethargy</td>
<td>69.70(58.85 80.57)</td>
<td>63.37(50.45 76.30)</td>
<td>64.90(55.39 74.41)</td>
<td>67(54.03 79.97)</td>
<td>0.440</td>
</tr>
<tr>
<td>Wind ( up or down)</td>
<td>57.87(45.85 69.94)</td>
<td>48.43(31.36 65.51)</td>
<td>55.16(43.07 67.25)</td>
<td>69.19(54.39 83.99)</td>
<td>0.336</td>
</tr>
<tr>
<td>Heartburn</td>
<td>25.41(13.10 37.73)</td>
<td>19.56(3.36 35.76)</td>
<td>20.42(10.64 30.20)</td>
<td>35.25(20.88 49.62)</td>
<td>0.544</td>
</tr>
<tr>
<td>Urinary symptoms</td>
<td>45.96(31.38 60.54)</td>
<td>36.44(16.78 56.10)</td>
<td>44.65(31.88 57.41)</td>
<td>58.37(40.84 75.91)</td>
<td>0.411</td>
</tr>
<tr>
<td>Thigh pain</td>
<td>34.9 (21.27 48.56)</td>
<td>25.00(11.02 38.98)</td>
<td>29.42(17.57 41.27)</td>
<td>23.37(9.43 37.32)</td>
<td>0.313</td>
</tr>
<tr>
<td>Muscle pain</td>
<td>41.66(27.20 56.13)</td>
<td>40.50(25.97 55.03)</td>
<td>42.23(30.26 54.19)</td>
<td>48.25(32.14 64.36)</td>
<td>0.910</td>
</tr>
<tr>
<td>Noncolonic score</td>
<td>214.02(181.70 246.34)</td>
<td>181.90(136.21 227.60)</td>
<td>197.76(167.56 227.95)</td>
<td>226.12(185.86 266.44)</td>
<td>0.223</td>
</tr>
</tbody>
</table>

Table 17 Noncolonic scores

The table above demonstrates the individual noncolonic scores in all the endometriosis patients and all the IBS patients compared to healthy volunteers. Results show that the endometriosis group scores are very similar to the IBS group.
All groups apart from the laparoscopy control group showed similar levels of anxiety with no significant differences. This may suggest that anxiety is not linked to symptoms or hypersensitivity. There is no evidence that patients with higher anxiety scores were more viscerally sensitive.
Figure 21 Depression scores

All groups had similar depression levels and those who were viscerally hypersensitive did not have higher depression scores than those who were hyposensitive or normosensitive. Visceral sensitivity results therefore, were not linked to depression scores.
Table 18 Mood

No significant differences were found in anxiety and depression scores among groups including the ROME positive endometriosis patients and the ROME negative patients.
5.5 DISCUSSION

With respect to demographic data it is of interest that the moderate to severe endometriosis group were the heaviest and compared to controls the difference was significant. A possible explanation for this finding is that, because this is a more severe group, they may have been subjected to more in the way of hormonal manipulation. However it was impossible to confirm this possibility as accurate data on hormonal manipulation and its duration was impossible to obtain from the patients record. Another interesting observation was that the IBS group was significantly less heavy than controls and their alcohol consumption and smoking habits were also significantly less that controls. This may be explained by the fact that because IBS is so difficult to control with medication, these patients resort to more “healthy” options, in addition the unit from which IBS patients were recruited, has a particular interest in dietary treatment of this condition and this may also explain the difference in weight between patients and controls.

Compared to controls, the endometriosis group as a whole exhibited a highly significant increase in noncolonic symptomatology, approximated to the prevalence of these symptoms in patients with IBS. When the endometriosis patients were then divided into ROME positive and ROME negative individuals, noncolonic symptoms tended to be more prevalent in the ROME positive patients than the ROME negative individuals; but this did not reach significance because the
numbers were relatively small. In the ROME positive, the prevalence of noncolonic symptoms was very similar to those with IBS. It has been previously suggested that enquiring about noncolonic symptoms might help separate the patients of IBS from other gastrointestinal disorders (205). However, the ability to use these symptoms to try to separate endometriosis from IBS is probably more confounded by the fact that so many patients with endometriosis fulfilled the criteria for IBS as mentioned before in Chapter Four. As can be seen from Table 17, the noncolonic symptomatology was greater in the ROME positive patients and it is likely that if the sample size had been much greater that some of these might have become significant. Although in clinical practice it is probable that enquiring about these symptoms may not be too helpful.

All patients in this study displayed significantly higher anxiety scores than the control population. However the achieved scores did not actually exceed the threshold for clinically significant anxiety and therefore, anxiety should not be considered as a problem in these individuals. The anxiety scores in the minimal to mild endometriosis group were the highest nearly matching those in the IBS group, although these differences were not significant. High anxiety scores but within the normal range are a typical feature of irritable bowel syndrome and this provides some weak circumstantial evidence that again irritable bowel syndrome might be driving some of the symptomatology in the minimal to mild endometriosis group.
Depression scores were not significantly different to controls, although the minimal to mild endometriosis matched the level found in irritable bowel syndrome. Although not significant, the group with the highest mean depression scores was the laparoscopy negative abdominal pain group and one might speculate that this might be due to the fact that they have not got a firm diagnoses.

These results again emphasise the difficulties in trying to distinguish between endometriosis and IBS as they do behave so similarly. However, at least recognising that this is such a problem may help clinicians, both gastroenterologists and gynaecologists, to manage these patients more satisfactorily.
CHAPTER SIX: DISCUSSION AND FUTURE RESEARCH
6.1 DISCUSSION

The results of the research presented in this thesis confirm the major problem of an overlap between the symptomatology of IBS and endometriosis and introduce a completely new paradigm of visceral hypersensitivity in endometriosis which offers the opportunity for the development of new and hopefully better treatment approaches.

Patients with endometriosis, irrespective of whether it is minimal to mild or moderate to severe, exhibit a high level of visceral hypersensitivity. This is likely to be of major importance in patients with minimal to mild disease who have severe symptoms and who are notoriously refractory to treatment. Irrespective of whether this clinical problem results from the visceral hypersensitivity amplifying their symptoms or is due to concurrent IBS, it might be better to attempt to treat these problems before embarking on more aggressive treatment approaches to endometriosis. Tri-cyclic antidepressants are one of the more effective treatments for IBS and this has been confirmed in a number of meta analyses (207). In addition these drugs also seem to have an effect in reducing visceral hypersensitivity. Therefore, the potential use of a tri-cyclic antidepressant in minimal to mild endometriosis would certainly be worth considering as the basis of a future clinical trial as this form of medication has activity against both IBS and visceral hypersensitivity.
It seems probable that more extensive endometriosis will produce symptoms of its own accord without the necessity to think about whether concurrent IBS is also contributory. However, the results presented here do show that patients with moderate to severe disease also exhibit visceral hypersensitivity and, therefore, it is possible that this could be amplifying the symptoms even in patients with more extensive disease. Therefore the use of tri-cyclic antidepressants could also be considered in this situation although addressing this in a clinical trial may be much more difficult due to the fact that there are likely to be many more confounding factors. One possible approach to taking all this forward would be to design a clinical trial in endometriosis where before initiating a tricyclic antidepressants, visceral hypersensitivity is assessed, as it has been in this study, to see if the degree of hypersensitivity is a predictor of response to treatment. As visceral sensitivity is regarded as such a critical component of IBS, it is likely that other pharmacological agents such as Pregabalin (208) and Ketotifen (98) may also have the potential to improve this abnormality. Consequently, any agent that has been shown to have activity against visceral hypersensitivity might be worthy of consideration for a trial of their potential in the treatment of endometriosis.

The presence of low grade mucosal inflammation in patients with IBS is the subject of intense investigation at the present time. It seems that at least a proportion of these patients have evidence of inflammation and various mechanisms have been suggested to account for this observation. These include previous episodes of gastroenteritis (50), previous use of antibiotics (209), and small bowel bacterial
overgrowth (210, 211). One hypothesis is that these all mediate their effect through subtle changes in the microbiota of the gut although at present it is not known whether such changes have an effect on visceral sensitivity. The potential benefit of probiotics in a variety of gastrointestinal conditions is now being extensively researched and irritable bowel syndrome is no exception to this rule. There is good evidence to suggest that some probiotic preparations do have beneficial effects in IBS and there is also now some preliminary data showing that they can have an effect on visceral sensitivity although, to date, these observations have mainly been in animals (212). If these data are supported in future studies then the potential effects of probiotics in endometriosis might be worth investigating. However, this would be dependent on the fact that probiotics not only reduce sensitivity in the gut, but elsewhere.

Inflammation has also been suggested to be implicated in the pathophysiology of endometriosis and if this is the case then seeking to reduce this in some way could be a possible therapeutic approach. It is now recognised that probiotics appear to have effects beyond the confines of the gut and, for instance, Bifidobacterium infantis 35624 has been shown have an effect on the balance between circulating anti-inflammatory and pro-inflammatory cytokines. Consequently the use of probiotics might influence cytokines or other inflammatory mediators (55, 213) that might possibly contribute to the inflammation associated with endometriosis and may be worthy of consideration in the future.
IBS is characterised by abdominal pain, abdominal bloating or distension and an abnormal bowel habit. In addition the majority of IBS patients also complain of a whole range of noncolonic symptoms of which lethargy, back pain, nausea and a variety of bladder symptoms are especially prominent. In the research presented in this thesis there is clearly a huge overlap in the symptomatology of IBS and endometriosis and unfortunately, no particular pattern of symptomatology seems to help to distinguish between the two conditions. Even bloating and distension were not useful discriminators. One of the more likely explanations for this confusion is the fact that symptoms consistent with the diagnosis of IBS were so prominent in patients with endometriosis. Consequently, any symptoms that are currently considered to be unique to IBS are likely to be present in many patients with endometriosis and therefore cannot be used for discriminating purposes making it very difficult to distinguish IBS and endometriosis on purely symptomatic grounds. Unfortunately, there are currently no other objective biomarkers for IBS and until such biomarkers are forthcoming the problem is likely to continue. The one symptom that might be more useful than others in helping to distinguish between the two conditions is an in depth enquiry about bowel habit because if a particular individual has especially severe diarrhoea or constipation, this is much more likely to be due to a bowel disorder than endometriosis. Unfortunately the number of patients with extreme disorders of bowel function in this study was insufficient for meaningful analysis on this point but this might be useful for future research using much larger numbers.
There are a number of limitations that need to be acknowledged in relation to the interpretation of these results on visceral hypersensitivity. One problem is that because IBS is a clinical diagnosis the patients in the IBS group are almost certainly not going to be homogenous although they did at least consistently exhibit visceral hypersensitivity which is an extremely common finding in this condition. Furthermore, it is entirely possible that some of the patients in the IBS group could have had endometriosis especially as endometriosis is such a common disorder but unfortunately, we were unable to obtain ethical approval to undertake laparoscopy in this group of patients. Consequently, the best we could do to try and decrease the chances of this confounding factor being too prominent was to at least exclude those with obvious gynaecological symptoms. It was felt important that some form of control group was included that could answer the question of whether just having a laparoscopy could lead to visceral sensitisation. Women undergoing laparoscopy for sterilisation were considered to be a good choice but there was one problem with this group. The same surgeon did not undertake the procedure in every case and it was, therefore, impossible to ensure that endometriosis was being sufficiently excluded in every patient as a detailed examination of the whole pelvis is not necessary for a routine sterilisation procedure. Furthermore, it would have been unacceptable for the research team to dictate surgical practice to gynaecologists who had no actual role in the study other than letting us recruit their patients.
A further confounding factor could be selection bias resulting from individuals with more prominent gastrointestinal symptoms volunteering for a study clearly interested in patients with gastrointestinal problems. This could therefore have resulted in more IBS patients being recruited to the study groups and consequently the finding of visceral hypersensitivity in many of these patients who also met the ROME criteria for the diagnosis of IBS. Lastly, we do not know whether the location of endometriosis, however minimal, might have an effect on rectal sensitivity as determined by a barostat. For instance, a patient with endometriosis on the serosal surface of their rectum may react completely differently to an individual with a similar sized lesion in another part of the pelvic peritoneal cavity.

Consequently, for all the above reasons, there is inevitably going to be a degree of heterogeneity in all of the patient groups participating in this study which indicates that the results need to be interpreted with some degree of caution.

None of the diagnostic techniques available for the investigation of the gastrointestinal system are useful in the investigation of IBS where the diagnosis is still totally dependent on symptom based criteria. In contrast at least laparoscopy accurately detects endometriosis but the question raised by this research is the possibility that it may not always be symptomatic and other factors such as visceral hypersensitivity in co-existent IBS could be important. Another concern is that gastroenterologists might be overlooking endometriosis that is sufficiently severe to require treatment as laparoscopy seldom forms part of their investigation.
Consequently, a very good case could be made for gastroenterologists and gynaecologists to be working much more closely together in order to provide the best management approach to these patients who have such similar and challenging symptoms.
6.2 FUTURE RESEARCH

The overlap between irritable bowel syndrome and endometriosis is clearly a major problem which can have an impact both on patients and the medical profession.

From the patient's point of view, it is important to get symptoms under control but the difficulties of finding out where these symptoms are coming from have been highlighted by this research. If it could be possible to identify enough endometriosis patients without the symptoms of IBS then comparing these patients with IBS patients might be helpful. However, if IBS symptoms are as common in other endometriosis populations as they were here, this approach may not be possible. It does appear that the treatment of IBS symptoms is probably associated with less in the way of adverse effects than the treatment of endometriosis, so in a patient with minimal disease the treatment of IBS symptoms may be initially worthwhile. At the same time, future clinical trials trying to identify the best treatment for this situation seem to be indicated. These should include studies on desensitising agents and possibly probiotics.

From the doctors' point of view, endometriosis is very unlikely to be missed by gynaecologists who are going to be alert to this possibility and have ready access to the methods for detecting the condition, although in some cases there can be a delay in diagnosis between the onset of symptoms and diagnosis of endometriosis.
of up to 7 years (214). However, gastroenterologists do not often arrange laparoscopies and, therefore, it is possible that the occasional patient with severe endometriosis is going to be wrongly diagnosed with IBS and if something like obstruction occurs then this could have serious consequences.

As has already been stated, a good case could be made for gynaecologists and gastroenterologists working much more closely together to try and develop better management strategies for this difficult clinical problem.

### 6.3 PUBLICATIONS ARISING FROM THIS WORK

Appendix 8.7 includes a copy of a paper published in GUT relating to visceral sensitivity and Appendix 8.8, has a copy of a paper published in Digestive Diseases and Sciences relating to abdominal distension.
6.4 CONCLUSION

Visceral hypersensitivity is very common among patients with endometriosis especially those with minimal-mild disease. This finding may explain why patients with mild endometriosis have severe pain as visceral hypersensitivity might be amplifying the pain in this group of patients. Therefore, their symptoms are often out of proportion to the extent of their disease. It could also be that IBS is actually the reason behind their pain, as a high percentage of patients with mild endometriosis studied have been found to fulfil the ROME III criteria.

It is likely that in many mild endometriosis patients, treating the visceral hypersensitivity or the IBS may prevent a range of gynaecological interventions. However, in others the endometriosis may need targeting and gynaecologists would welcome a method of identifying such individuals. The results of this study might be highly significant as by simply measuring visceral sensation in these patients, viscerally hypersensitive patients can be identified. They may then be treated by desensitising agents such as tricyclic antidepressants (TCAs) which is a completely different treatment pathway from the one which is currently used such as hormonal manipulation or various surgical interventions.

This study, therefore, has introduced a completely new method for treating patients with mild endometriosis.
REFERENCES


APPENDIXES

Appendix 1  The Hospital Anxiety Depression (HAD) Scale (206),

Appendix 2  The ROME III diagnostic questionnaire (73),

Appendix 3  The irritable bowel syndrome’ Symptom Severity Score IBS SSS (203)

Appendix 4  Quality of life Questionnaire (72)

Appendix 5  The Non-colonic Symptom score (198).

Appendix 6  Barostat Operating Procedure

Appendix 7  Visceral hypersensitivity in endometriosis: a new target for treatment?

Appendix 8  Abdominal bloating and distension: what is the role of the microbiota
8.1 IBS SEVERITY SCORE QUESTIONNAIRE (APPENDIX)

IBS SEVERITY SCORE QUESTIONNAIRE

INSTRUCTIONS

This form is designed to enable us to record and monitor the severity of your IBS. It is to be expected that your symptoms might vary over time, so please try and answer the questions based on how you currently feel (ie over the last 10 days or so). All information will be kept in strict confidence.

1. For questions where a number of different responses are a possibility please circle the response appropriate to you.

2. Some questions will require you to write in an appropriate response.

3. Some questions require you to put a cross on a line, which enables us to judge the severity of a particular problem.

For example:

How severe was your pain?

Please place your cross (X) anywhere on the line between 0-100% in order to indicate as accurately as possible the severity of your symptom.

This example shows a severity of approximately 90%

0% ___________________________________ X 100%  
no pain            not very severe        quite severe  severe  very severe
PART 1: SEVERITY SCORE

1. a) Do you currently suffer from abdominal (tummy) pain?  
   YES ☐ NO ☐
   Circle appropriate box

   b) If yes, how severe is your abdominal (tummy) pain?
   0% | 100%
   no pain | not very severe | quite severe | severe | very severe

   c) Please enter the number of days that you get the pain in every 10 days.
   For example if you enter 4 it means that you get pain 4 out of 10 days. If you get pain every day enter 10
   Number of days with pain ☐ ☐ x10 ☐

2. a) Do you currently suffer from abdominal distension* 
   (bloating, swollen or tight tummy)  
   YES ☐ NO ☐
   Circle appropriate box
   (*women, please ignore distension related to your periods)

   b) If yes, how severe is your abdominal distension/tightness
   0% | 100%
   no distension | not very severe | quite severe | severe | very severe

3. How satisfied are you with your bowel habit?
   0% | 100%
   very happy | quite happy | unhappy | very unhappy

4. Please indicate with a cross on the line below how much your Irritable Bowel Syndrome is affecting or interfering with your life in general
   0% | 100%
   not at all | not much | quite a lot | completely

IBS SEVERITY SCORE: ☐
8.2 HOSPITAL ANXIETY AND DEPRESSION

QUESTIONNAIRE (HAD) (APPENDIX)

Please complete each of the following questions, checking the one response that comes closest to how you have been feeling in the past week.

I feel tense or ‘wound up’:

1  □  Most of the time
2  □  A lot of the time
3  □  Sometimes
4  □  Never

I still enjoy the things I used to enjoy:

1  □  Definitely as much
2  □  Not quite as much
3  □  Only a little
4  □  Hardly at all

I get a sort of frightened feeling as if something awful is about to happen:

1  □  Definitely and quite badly
2  □  Yes, but not too badly
3  □  A little, but it doesn’t worry me
4  □  Never

I can laugh and see the funny side of things:

1  □  As much as I always could
2  □  Not quite as much now
3  □  Definitely not as much now
4  □  Never

Worrying thoughts go through my mind:

1  □  All of the time
2  □  A lot of the time
3  □  Sometimes, but not too often
4 □ Rarely

I feel cheerful:

1 □ Never
2 □ Not often
3 □ Sometimes
4 □ Most of the time

I can sit at ease and feel relaxed:

1 □ Definitely
2 □ Usually
3 □ Not often
4 □ Never

I feel as if I am slowed down:

1 □ Nearly all the time
2 □ Very often
3 □ Sometimes
4 □ Never

I get a sort of frightened feeling like ‘butterflies’ in the stomach:

1 □ Never
2 □ Occasionally
3 □ Quite often
4 □ Very often

I have lost interest in my appearance:

1 □ Definitely
2 □ I don’t take as much care as I should
3 □ I may not take quite as much care
4 □ I take just as much care as ever

I feel restless, as if I have to be on the move:

1 □ Very much
2 □ Quite a lot
3 □ Not Very much
4 □ Never
I look forward with enjoyment to things:

1 □ As much as I ever did  
2 □ Somewhat less than I used to  
3 □ Definitely less than I used to  
4 □ Hardly at all

I get sudden feelings of panic:

1 □ Very often  
2 □ Quite often  
3 □ Not very often  
4 □ Never

I can enjoy a good book or TV program:

1 □ Often  
2 □ Sometimes  
3 □ Not often  
4 □ Rarely

Thank you very much for taking the time to fill in this questionnaire.

Please check that you have answered all the questions.
### 8.3 ROME III QUESTIONNAIRE (APPENDIX)

<table>
<thead>
<tr>
<th><strong>Functional Bowel Disorders</strong></th>
<th><strong>Question</strong></th>
<th><strong>Options</strong></th>
<th><strong>Skip to question 9</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IBS</strong></td>
<td>1. In the last 3 months, how often did you have discomfort or pain anywhere in your abdomen?</td>
<td>① Never ② Less than one day a month ③ One day a month ④ Two to three days a month ⑤ One day a week ⑥ More than one day a week ⑦ Every day</td>
<td></td>
</tr>
<tr>
<td><strong>2.</strong></td>
<td>For women: Did this discomfort or pain occur only during your menstrual bleeding and not at other times?</td>
<td>① No ② Yes ③ Does not apply because I have had the change in life (menopause) or I am a male</td>
<td></td>
</tr>
<tr>
<td><strong>3.</strong></td>
<td>Have you had this discomfort or pain 6 months or longer?</td>
<td>① No ② Yes</td>
<td></td>
</tr>
<tr>
<td><strong>4.</strong></td>
<td>How often did this discomfort or pain get better or stop after you had a bowel movement?</td>
<td>① Never or rarely ② Sometimes ③ Often ④ Most of the time ⑤ Always</td>
<td></td>
</tr>
<tr>
<td><strong>5.</strong></td>
<td>When this discomfort or pain started, did you have more frequent bowel movements?</td>
<td>① Never or rarely ② Sometimes ③ Often ④ Most of the time ⑤ Always</td>
<td></td>
</tr>
<tr>
<td><strong>6.</strong></td>
<td>When this discomfort or pain started, did you have less frequent bowel movements?</td>
<td>① Never or rarely ② Sometimes ③ Often ④ Most of the time ⑤ Always</td>
<td></td>
</tr>
<tr>
<td><strong>7.</strong></td>
<td>When this discomfort or pain started, were your stools (bowel movements) looser?</td>
<td>① Never or rarely ② Sometimes ③ Often ④ Most of the time ⑤ Always</td>
<td></td>
</tr>
<tr>
<td><strong>8.</strong></td>
<td>When this discomfort or pain started, how often did you have harder stools?</td>
<td>① Never or rarely ② Sometimes ③ Often ④ Most of the time ⑤ Always</td>
<td></td>
</tr>
<tr>
<td><strong>9.</strong></td>
<td>In the last 3 months, how often did you have fewer than three bowel movements (0-2) a week?</td>
<td>① Never or rarely ② Sometimes ③ Often ④ Most of the time ⑤ Always</td>
<td></td>
</tr>
<tr>
<td><strong>10.</strong></td>
<td>In the last 3 months, how often did you have hard or lumpy stools?</td>
<td>① Never or rarely ② Sometimes ③ Often ④ Most of the time ⑤ Always</td>
<td>Alternative scale: ① Never or rarely ② About 25% of the time ③ About 50% of the time ④ About 75% of the time ⑤ Always, 100% of the time</td>
</tr>
<tr>
<td>Question</td>
<td>Options</td>
<td>Alternative Scale</td>
<td></td>
</tr>
<tr>
<td>------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------</td>
<td>-----------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>11. In the last 3 months, how often did you strain during bowel movements?</td>
<td>Never or rarely, Sometimes, Often, Most of the time, Always</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12. In the last 3 months, how often did you have a feeling of incomplete emptying after bowel movements?</td>
<td>Never or rarely, Sometimes, Often, Most of the time, Always</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13. In the last 3 months, how often did you have a sensation that the stool could not be passed, (i.e., blocked), when having a bowel movement?</td>
<td>Never or rarely, Sometimes, Often, Most of the time, Always</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14. In the last 3 months, how often did you press on or around your bottom or remove stool in order to complete a bowel movement?</td>
<td>Never or rarely, Sometimes, Often, Most of the time, Always</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15. Did any of the symptoms of constipation listed in questions 9-14 above begin more than 6 months ago?</td>
<td>No, Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16. In the last 3 months, how often did you have loose, mushy or watery stools?</td>
<td>Never or rarely → Skip to question 19, Sometimes, Often, Most of the time, Always</td>
<td>Alternative scale: Never or rarely, About 25% of the time, About 50% of the time, About 75% of the time, Always, 100% of the time</td>
<td></td>
</tr>
<tr>
<td>17. In the last 3 months, were at least three fourths (3/4) of your stools loose, mushy or watery?</td>
<td>No, Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18. Did you begin having frequent loose, mushy, or watery stools more than 6 months ago?</td>
<td>No, Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>19. In the last 3 months, how often did you have bloating or distension?</td>
<td>Never → Less than one day a month, One day a month, Two to three days a month, One day a week, More than one day a week, Every day</td>
<td>Skip remaining question</td>
<td></td>
</tr>
<tr>
<td>20. Did your symptoms of bloating or distension begin more than 6 months ago?</td>
<td>No, Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>21.</td>
<td>In the last 3 months, how often did you feel uncomfortably full after a regular-sized meal?</td>
<td>① Never → ② Less than one day a month ③ One day a month ④ Two to three days a month ⑤ One day a week ⑥ More than one day a week ⑦ Every day</td>
<td>Skip to question 23</td>
</tr>
<tr>
<td>22.</td>
<td>Have you had this uncomfortable fullness after meals 6 months or longer?</td>
<td>① No ② Yes</td>
<td></td>
</tr>
<tr>
<td>23.</td>
<td>In the last 3 months, how often were you unable to finish a regular size meal?</td>
<td>① Never → ② Less than one day a month ③ One day a month ④ Two to three days a month ⑤ One day a week ⑥ More than one day a week ⑦ Every day</td>
<td>Skip to question 25</td>
</tr>
<tr>
<td>24.</td>
<td>Have you had this inability to finish regular size meals 6 months or longer?</td>
<td>① No ② Yes</td>
<td></td>
</tr>
<tr>
<td>25.</td>
<td>In the last 3 months, how often did you have pain or burning in the middle of your abdomen, above your belly button but not in your chest?</td>
<td>① Never → ② Less than one day a month ③ One day a month ④ Two to three days a month ⑤ One day a week ⑥ More than one day a week ⑦ Every day</td>
<td>Skip remaining question</td>
</tr>
<tr>
<td>26.</td>
<td>Have you had this pain or burning 6 months or longer?</td>
<td>① No ② Yes</td>
<td></td>
</tr>
</tbody>
</table>

C. Functional Bowel Disorders

**C1. Irritable Bowel Syndrome**

**Diagnostic Criteria***

Recurrent abdominal pain or discomfort** at least 3 days/month in last 3 months associated with two or more of criteria #1 - #3 below:

*Pain or discomfort at least 2-3 days/month (question 1>2)*

For women, does pain occur only during menstrual bleeding? (question 2=0 or 2)

Improvement with defecation

*Pain or discomfort gets better after BM at least sometimes (question 4>0)*

Onset associated with a change in frequency of stool

Onset of pain or discomfort associated with more stools at least sometimes (question 5>0), OR
Onset of pain or discomfort associated with fewer stools at least sometimes (question 6>0)

Onset associated with a change in form (appearance) of stool

Onset of pain or discomfort associated with looser stools at least sometimes (question 7>0), OR
Onset of pain or discomfort associated with harder stools at least sometimes (question 8>0)
* Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis
  Yes. (question 3=1)

**"Discomfort" means an uncomfortable sensation not described as pain.

In pathophysiology research and clinical trials, a pain/discomfort frequency of at least two days a week is recommended for subject eligibility.

Pain or discomfort more than one day per week (question 1=4)

Criteria for IBS-C
question 10>0 and question 16=0.

Criteria for IBS-D
question 10=0 and question 16>0.

Criteria for IBS-M
question 10>0 and question 16=0.

Criteria for IBS-U
question 10=0 and question 16=0.

C2. Functional Bloating

Diagnostic criteria*

Must include all of the following:

Recurrent feeling of bloating or visible distension at least 3 days/month in 3 months

Bloating or distension at least 2-3 days/month (question 19>2)

There are insufficient criteria for a diagnosis of functional dyspepsia.

Insufficient criteria for functional dyspepsia

[(question 13<5) OR (question 14=0)], AND
[(question 15<5) OR (question 16=0)], AND
[(question 17<5) OR (question 18=0)]

There are insufficient criteria for a diagnosis of irritable bowel syndrome or functional constipation.

* Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis
  Yes. (question 19=1)

C3. Functional Constipation

Diagnostic criteria*

Must include two or more of the following:

Straining during at least 25% of defecations
  At least often. (question 11>1)

b) Lumpy or hard stools at least 25% of defecations
  At least often. (question 10>1)

c) Sensation of incomplete evacuation at least 25% of defecations
  At least sometimes. (question 12>0)

d) Sensation of anorectal obstruction/blockage at least 25% of defecations
  At least sometimes. (question 13>0)
e) Manual maneuvers to facilitate at least 25% of defecations (e.g., digital evacuation, support of the pelvic floor)
   
   At least sometimes. (question 14=0)

f) Fewer than three defecations per week

   At least often. (question 9=1)

Loose stools are rarely present without the use of laxatives.

Loose stools occur never or rarely (question 7=0), &

Insufficient criteria for IBS

* Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis

Yes. (question 15=1)

C4. Functional Diarrhea

Diagnostic Criterion*

Loose (mushy) or watery stools without pain occurring at least 75% of stools AND

Watery stools at least ¼ of time (question 17=1)

Pain or discomfort never occurs (question 1=0)

* Criterion fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis

Yes. (question 18=1)
8.4 QUALITY OF LIFE QUESTIONNAIRE (APPENDIX)

11. a) How well are you coping with problems?

<table>
<thead>
<tr>
<th>0%</th>
<th>100%</th>
</tr>
</thead>
<tbody>
<tr>
<td>not at all</td>
<td>very well</td>
</tr>
</tbody>
</table>

b) How confident and secure do you feel in yourself?

<table>
<thead>
<tr>
<th>0%</th>
<th>100%</th>
</tr>
</thead>
<tbody>
<tr>
<td>very bad</td>
<td>all the time</td>
</tr>
</tbody>
</table>

c) How well are you sleeping?

<table>
<thead>
<tr>
<th>0%</th>
<th>100%</th>
</tr>
</thead>
<tbody>
<tr>
<td>not at all</td>
<td>very well</td>
</tr>
</tbody>
</table>

d) How often are you irritable?

<table>
<thead>
<tr>
<th>0%</th>
<th>100%</th>
</tr>
</thead>
<tbody>
<tr>
<td>always</td>
<td>never</td>
</tr>
</tbody>
</table>

e) How often do you worry?

<table>
<thead>
<tr>
<th>0%</th>
<th>100%</th>
</tr>
</thead>
<tbody>
<tr>
<td>always</td>
<td>never</td>
</tr>
</tbody>
</table>

f) How much are you able to enjoy life?

<table>
<thead>
<tr>
<th>0%</th>
<th>100%</th>
</tr>
</thead>
<tbody>
<tr>
<td>not at all</td>
<td>can enjoy life to the full</td>
</tr>
</tbody>
</table>

g) How much do you rate your feelings of hopefulness?

<table>
<thead>
<tr>
<th>0%</th>
<th>100%</th>
</tr>
</thead>
<tbody>
<tr>
<td>not at all</td>
<td>very hopeful</td>
</tr>
</tbody>
</table>

h) Physically how well do you feel

<table>
<thead>
<tr>
<th>0%</th>
<th>100%</th>
</tr>
</thead>
<tbody>
<tr>
<td>very bad</td>
<td>very good</td>
</tr>
</tbody>
</table>

i) How well would you rate your relationship with others?

<table>
<thead>
<tr>
<th>0%</th>
<th>100%</th>
</tr>
</thead>
<tbody>
<tr>
<td>poor</td>
<td>excellent</td>
</tr>
</tbody>
</table>

SUB TOTAL: [ ]
f) How would you rate your ability to maintain friendship:

0% poor
100% excellent

k) How would you rate your feelings of inferiority?

0% very inferior
100% no feelings of inferiority

l) How much do you feel wanted?

0% not at all
100% very wanted

m) Do you ever feel helpless and not in control of your life?

0% all the time
100% in full control

n) How much difficulty do you have making decisions?

0% Can't make any decisions
100% No difficulties at all

o) How much do you rate your enjoyment of leisure time?

0% very poor
100% enjoy to the full

SUB TOTAL:

ILLNESS IMPACT SCORE divided by 3:
8.5 NONCOLONIC QUESTIONNAIRE (APPENDIX)
PART 3: NON-COLONIC FEATURES

10. Do you suffer from the following:

a) Nausea/vomiting?
   - 0% never
   - 100% all the time

b) Difficulty finishing meals?
   - 0% never
   - 100% all the time

c) Headaches?
   - 0% never
   - 100% all the time

d) Backache?
   - 0% never
   - 100% all the time

e) Lethargy or tiredness?
   - 0% never
   - 100% all the time

f) Excess wind (up or down)?
   - 0% never
   - 100% all the time

g) Heartburn?
   - 0% never
   - 100% all the time

h) Having to pass urine frequently or with urgency
   - 0% never
   - 100% all the time

i) Thigh pain
   - 0% never
   - 100% all the time

j) Aches and pains in your muscles and joints
   - 0% never
   - 100% all the time

NON COLONIC SCORE divided by 2: 

5
8.6 BAROSTAT STANDARD OPERATING PRESSURE

(APPENDIX)

1. Pre-procedure

Before visit remind patient to fast overnight and abstain from strenuous exercise beforehand and Check you have everything: gown, Fleet enema, KY gel, gauze swabs, catheter, micropore tape, patient file, clipboard, pen, Sensation explanation notes. Switch the computer then the Barostat and leave the Barostat machine to warm up for approx 1hr prior to being used.

2. When the Patient arrives

Explain the test to them and answer any questions they may have and Check they have complied with the fasting restrictions. Run through the visit check list (BP, Questionnaires etc) and give the patient a gown, ask to lie on the bed on LHS with knees bent.

If patient has not administered enema at home, ask them to do it then. After the patient has emptied their bowels get them to lie on the bed to allow the gut to relax for approx 20 minutes. While patient is relaxing calibrate Barostat (Section 4)

3. Catheter insertion
Perform PR then fold the balloon neatly around the catheter and cover the end in KY jelly. Insert the catheter slowly as far as the blue marking. During this process ask the patient to concentrate on their breathing.

Leave the tube disconnected from the Barostat until the test starts (approx 20-30 minutes after catheter insertion).

4. Calibration

Double click on Protocol (5.11) and in patient procedure section, click on RUN PROTOCOL. On the Barostat associated box key pad press (key1), (enter/go). This homes the piston then press (vol offset/8), (0), (enter/go). This zeros the display.

Test for overpressure by connecting the Sphyg to the Balloon Port on the front of the Barostat and press (2), (20), (enter/go), (enter/go). The mercury on the sphyg should not rise above 80mmHg. DO NOT USE if pressure is <80mmHg.

Disconnect the sphyg and home the piston again (key1), (enter/go). If it does not return to zero then press (vol offset/8), (0), (enter/go).

Connect the Balloon Port and Measurement Port together (both ports are located on the front left hand side of the Barostat) with a piece of tubing.
Press (2), (20), (enter/go) (enter/go) to set the pressure at 20mmHg. Note down the Pressure and Volume values on the Barostat, once they have stopped rising.

Leave for 5-10mins. Pressure value should stay (roughly 20mmHg) and Volume values (40). Press (clear/halt) and disconnect tubing.

Home the piston again (key1), (enter/go). If it does not return to zero then repeat the step above by pressing (vol offset/8), (0), (enter/go).

Set the piston at 50ml by pressing (vol offset /8), (50), (►◄) and check that the vol = 50ml (roughly) on the Barostat. After this zero the display by pressing (vol offset/8), (0), (enter/go).

On the RUN PROTOCOL screen on the computer, press (Calibrate) on the bottom left hand side of the screen and then press (Yes).

5. Update Patient details

Go to Main Menu, Patient procedure section, Experiment Set Up and update patient details, NAME, DOB, SEX and PATIENT STUDY ID NUMBER

Hit “SAVE AS” button and change RESULTS file name to include Patient initials, patient number and group type.

6. Barostat Procedure
LOAD PROTOCOL and SELECT C:\ Barostat\dis\waBOP. Save results file as endo JS64IBS if not saved before and file Index is always 1.

Go to MAIN MENU and then connect catheter to machine (M = Measurement port, B= Balloon port) before running the protocol “RUN PROTOCOL”

Measure BOP: At 1min intervals ask patient to take a deep breath in and cough. Watch the trace and when you see a peak press F4 (STOP).

Program this pressure point at F4 as this is the patients baseline pressure (BOP) and allow the patient 8 - 10mins rest. Press STOP and enter the BOP into the Preset Pressure Box next to the F4 Button.

Above main window-open file: wadisbop12 and Run Protocol. Tell the patient the test proper is about to start and that they will feel increasing sensations. Give them the scoring card. Pressure/volume will increase incrementally from the BOP.

Look out for the Red prompt button, and then ask patient for their score for Stool and pain sensations. Note down on sheet.

Press 1 on small box, if sensation score was < 3 for pain. However, when Pain reaches 3, or more press the RH end button (the white square) instead.

Do a total of 12 readings (pressure will increase up to pain 3 then oscillates about this point). Change F4 to 0 then press STOP.
Press HOME (top RHS of screen) as this empties the balloon completely setting pressure to zero. Disconnect catheter tubes from the measurement port and balloon port and switch OFF Barostat before pressing on Exit from MAIN MENU on computer screen.

Remove the catheter and dispose then check that patients are okay before they leave the unit.
8.7 VISCERAL HYPERSENSITIVITY IN ENDOMETRIOSIS:
A NEW TARGET FOR TREATMENT (APPENDIX)
Visceral hypersensitivity in endometriosis: a new target for treatment?

B Issa, T S Onon, A Agrawal, C Shekhar, J Morris, S Hamdy, P J Whorwell

ABSTRACT
Objective In women presenting to gynaecological clinics with lower abdominal pain, the cause is frequently attributed to endometriosis irrespective of whether it is found to be minimal or extensive at laparoscopy. Irritable bowel syndrome (IBS) is also common in this setting, and it was speculated that the visceral hypersensitivity associated with this condition might be amplifying the symptoms of endometriosis.

Methods Visceral sensitivity to balloon distension, symptoms and psychological status were assessed following laparoscopy in 20 women with minimal to mild endometriosis, 20 with moderate to severe endometriosis, 20 with laparoscopy negative abdominal pain and 20 asymptomatic women undergoing laparoscopic sterilisation who acted as controls, and compared with 20 women with IBS.

Results Compared with controls, patients with minimal to mild and moderate to severe endometriosis had a higher prevalence of symptoms consistent with IBS (0% vs 65% and 50%, respectively, p<0.001) with significantly lower mean pain thresholds (39.5 mm Hg (95% CI 38.0 to 43.0) vs 26.1 mm Hg (95% CI 24.5 to 27.7), p=0.001 and 26.6 mm Hg (95% CI 24.9 to 28.3), p=0.002) not explained by differences in rectal compliance. Patients with laparoscopy negative pain had symptoms and visceral sensitivity similar to patients with IBS. Controls undergoing laparoscopy had normal sensitivity, indicating that the laparoscopic procedure was not inducing hypersensitivity.

Conclusion Visceral hypersensitivity is extremely common in endometriosis and could be intensifying the pain. This finding might explain why mildly affected individuals often complain of severe symptoms out of proportion to the extent of their disease. This study has introduced a completely new concept into the understanding of pain in endometriosis and could open up new opportunities for treatment.

INTRODUCTION
We have previously shown that patients with irritable bowel syndrome (IBS) frequently have a wide range of non-colonic symptoms such as backache and lethargy as well as a number of musculoskeletal, urological and gynaecological problems. These can result in patients being referred to the wrong specialty if the gastrointestinal symptoms are not severe or a non-colonic feature is especially prominent. This is a particular problem in gynaecological clinics as women with IBS often have dysmenorrhoea and dyspareunia, making referral to this setting even more likely. We have also shown that patients with IBS are over-represented in gynaecological clinics with outcomes being less favourable in these individuals, and it is also noteworthy that hysterectomy rates are much higher in patients with IBS.

In women presenting to gynaecological practice with abdominal or pelvic pain, the investigation frequently includes laparoscopy and endometriosis is not an unusual finding. This is perhaps not surprising as it is a common condition and can even be found in up to 10% of asymptomatic individuals. If the condition is severe it seems reasonable to conclude that it causes symptoms, but if it is mild this may not be such a safe conclusion. However, in patients with lower abdominal pain it is common gynaecological practice to attribute the pain to endometriosis, whatever the severity. This may be a critically important factor in a patient who actually has IBS and is being referred to the gynaecologist because of coincidental gynaecological symptoms such as heavy periods or dyspareunia, especially as the latter is a common feature in IBS. In such a situation, laparoscopically minimal endometriosis might wrongly be implicated as the cause of the pain.
minimal endometriosis might wrongly be implicated as the cause of the pain. There are at least two potential ways in which IBS and endometriosis might be confused. First, it has been known for many years that IBS is frequently associated with excessive sensitivity to balloon distension of the gut, which is usually referred to as visceral hypersensitivity.\(^\text{14}\) To the extent that it has even been suggested by some that it might be a biological marker for the condition.\(^\text{15}\) Consequently, it may be possible that, in an individual with IBS and visceral hypersensitivity, a small area of endometriosis which would not normally be perceived as painful might become painful as a result of amplification of any subminal pain associated with the lesion. Alternatively, the pain in a patient with minimal endometriosis might be due to coexisting IBS with the endometriosis being a coincidental finding which is not directly causing any problems. Indeed, there are reports of IBS being associated with endometriosis,\(^\text{14}\) but these observations do not answer the question of whether this is due to symptom amplification or the coincidence of two separate conditions. Either of these two hypotheses might explain why it is frequently reported that the intensity of the pain in endometriosis appears to bear little or no relationship to the severity of disease as determined by laparoscopy,\(^\text{16}\) with mildly affected patients in particular often complaining of the most pain. In such individuals the finding of mild endometriosis could currently lead to a series of pharmacological treatments such as hormonal manipulation or, in the absence of a response, some form of surgical intervention. We have speculated that visceral hypersensitivity might be contributing to the pain experienced by women with endometriosis and, when the condition is mild, may lead to inappropriate treatment. The purpose of this study was therefore to assess the prevalence of visceral hypersensitivity in patients with varying degrees of endometriosis as well as documenting symptoms consistent with a diagnosis of IBS.

**METHODS**

Patients attending the gynaecological department for the laparoscopic investigation of abdominal pain and found to have endometriosis were eligible for the study. Those without any evidence of other coexistent gynaecological disease had their endometriosis carefully documented and staged according to the Revised American Fertility Society (RAPS) guidelines,\(^\text{17}\) which recommend reporting the laparoscopic findings as minimal, mild, moderate or severe based on a points system that takes into account the size and site of the lesions and the extent of adhesions and cul-de-sac obliteration. The RAPS guidelines were selected because they are the most widely accepted system, although it has to be acknowledged that all staging systems for endometriosis are subjective and therefore prone to interobserver variation. Patients were then divided into two groups consisting of 20 with minimal to mild endometriosis and 20 with moderate to severe disease, and these were compared with three other groups of women: (1) 20 patients attending for diagnostic laparoscopy for the investigation of abdominal pain and found to have a normal pelvis formed a group of individuals with laparoscopically negative abdominal pain; (2) 20 patients attending for laparoscopic sterilisation were included as a group of laparoscopically normal healthy volunteers in order to investigate the possibility that laparoscopy might lead to visceral sensitisation; and (3) 20 women with a firm diagnosis of uncomplicated IBS although, for ethical reasons, we were not allowed to undertake laparoscopy in these individuals. Participants taking long-term medication likely to affect visceral sensation were excluded as were those unable to stop taking for a period of 48 h any other medication that could possibly interfere with the results (eg, analgesics, antispasmodics, antidepressants or non-steroidal anti-inflammatory preparations). All barostat tests were carried out in the luteal phase of the menstrual cycle in those individuals with regular periods at least 4 weeks after their laparoscopy.

All subjects completed the following questionnaires: the Hospital Anxiety Depression (HAD) Scale,\(^\text{18}\) the Rome II diagnostic questionnaire,\(^\text{19}\) the Irritable Bowel Syndrome Symptom Severity Score (IBS SSS)\(^\text{20}\) and the Non-Colonic Symptoms and Quality of Life Score.\(^\text{21}\) The only validated symptom severity scoring system for endometriosis was published after the start of this study\(^\text{22}\) and therefore not used. However, the following symptoms and other features associated with endometriosis were recorded: pain severity with periods graded on a scale of 0–10, pain on intercourse graded on a scale of 0–10, pain severity between periods graded on a scale of 0–10, parity, difficulty conceiving before work due to pain, continuing at work despite pain and a family history of endometriosis. Those items that were scored 0–10 were combined into an overall endometriosis pain score (0–80) and used for the analysis. Any other relevant medical data were also recorded.

Rectal sensitivity testing is a well-described technique\(^\text{23}\) which was performed after an overnight fast and a clear liquid diet. All participants being asked to refrain from smoking and the consumption of caffeine for 24 h. Sensitivity was assessed using a barostat technique with tracking which has been described in detail elsewhere.\(^\text{24}\) A flexible barostat bag was placed in the rectum and the participant allowed to rest for 1 h. Isobaric phase distensions were then performed (increments of 4 mm Hg for 1 min with 1 min rest at each step) up to a maximum pressure of 50 mm Hg. At each step the volume of the bag was measured in order to build dynamic compliance curves. In addition, anorectal compliance was calculated by taking the mean value of the volume of the barostat at a pressure of 20 mm Hg. The patient was questioned at each inflation step (4 mm Hg) in order to find the amount of distension associated with the first sensation of distension, sensation of stool and sensation of pain. During each inflation above basal operating pressure levels, 30 s after commencement of the inflation, patients were prompted to indicate on a standard proforma what sensations they were experiencing. Tracking, which is a technique which makes the inflations unpredictable to the subject and thus minimises bias, was commenced when the subject first experienced moderate or severe pain. Subsequent distensions were then adjusted up or down, depending on the subject's response to the previous distension. If the subject reported pain on the previous trial, the next distension was decreased or kept the same. If the subject reported no pain on the previous trial, the next distension was increased or kept the same. In order to make the changes in the amount of distension unpredictable, a random numbers algorithm was used to determine whether to decrease the amount of distension or keep it the same following a painful test period. The sensory threshold was then determined by averaging the intensity over a series of tracking trials of the threshold. The distension test was discontinued after 12 distension trials or after reaching the upper limit of 50 mm Hg without pain sensation. At any time the patient could choose to terminate the distension session for any reason by pressing the 'panic button'. The investigator could also stop the test if it was considered undesirable to continue for any reason.

**Power calculation**

Based on previous data collected in our laboratory on visceral sensation using rectal sensitivity testing, it was estimated that
this study would require 20 patients in each endometriosis and control group in order to have an 80% power of detecting a difference in sensitivity of 10 mm Hg between groups at a significance level of 5%.

Statistical analysis
Comparisons between patient groups were carried out using one-factor ANOVA followed by the Scheffé multiple comparison test. Anxiety and depression scores followed a non-normal distribution, and for these variables, the non-parametric Kruskal–Wallis test was used followed by the Mann–Whitney U test with Bonferroni correction. The influence of anxiety and depression on group comparisons was assessed by analyses of covariance. The results of analyses of covariance, when adjusted for anxiety and depression, did not differ from those from the simple ANOVA and are therefore not reported. The relationship between pain thresholds and IBS severity scores as well as endometriosis pain scores were assessed using the Pearson correlation coefficient. Pain thresholds were compared in patients with Rome positive and Rome negative endometriosis using the independent t test. The same statistics were used for comparing the endometriosis pain scores in patients with minimal to mild and moderate to severe endometriosis.

RESULTS
Table 1 shows the demographic and clinical data for each of the groups, whether the patients fulfilled the Rome criteria for IBS and, if so, the type (constipation, diarrhoea, mixed or unclassified). Also shown are the scores for anxiety, depression, IBS severity and quality of life.

Table 2 shows the results of barostat testing for sensory thresholds and compliance. All groups were comparable with respect to age but there were significant differences in other variables. As might be expected, the healthy controls did not meet the criteria for IBS and had sensory thresholds within the normal range.

In comparison with the controls, all the other groups had a higher prevalence of symptoms consistent with IBS as well as elevated IBS symptom severity scores. With regard to pain thresholds, all groups except those patients with abdominal pain without any other abnormality had hypersensitivity similar to that seen in IBS, which was significantly different from that seen in controls. The thresholds for first sensation and stool sensation showed similar trends. Figure 1 shows the mean values and individual data for pain thresholds for all groups studied. There was a highly significant difference in the thresholds for pain in the endometriosis groups compared with the controls (p=0.001 and p=0.002, respectively, for minimal to mild and moderate to severe endometriosis). It is important to note that the controls who had undergone laparoscopy for reasons other than pain had normal sensitivity (table 1 and figure 1). This indicates that the process of having a laparoscopic procedure is not in itself the cause of the hyperalgesia observed in the other groups. There were no significant differences between the groups with respect to rectal compliance.

A 90% normal reference range for sensitivity was derived for the laparoscopic controls and found to be 31–48 mm Hg. Based on this, 60% (12/20) of the patients with minimal to mild endometriosis and 65% (13/20) of those with moderate to severe endometriosis had pain thresholds below the lower limit of this range. In addition, 75% (15/20) of the patients with IBS and 45% (9/20) of the patients with laparoscopy negative pain had sensitivity below this range.

With regard to IBS severity and pain thresholds in all groups, there was only a significant correlation between severity and pain threshold in the moderate to severe endometriosis group (r=−0.47; p=0.036). When patients with endometriosis were divided into those fulfilling or not fulfilling the Rome criteria for IBS, there was no significant difference in the mean pain thresholds for the minimal to mild cases. However, among the patients with moderate to severe endometriosis, the Rome-positive patients had significantly lower mean pain thresholds than the Rome-negative individuals (24.6 mm Hg vs 33.8 mm Hg; p=0.003).

With regard to the endometriosis pain scores, there was no significant difference between patients with minimal to mild disease and those with moderate to severe disease (mean score 11.00 vs 11.6; p=0.75). Furthermore, there was no significant correlation between the endometriosis pain scores and pain thresholds for any of the endometriosis groups.

DISCUSSION
This study has introduced a completely new concept into the understanding of pain in endometriosis. It appears that visceral

Table 1  Demographic and clinical data

<table>
<thead>
<tr>
<th></th>
<th>Laparoscopy controls (n = 20)</th>
<th>Minimal to mild endometriosis (n = 20)</th>
<th>Moderate to severe endometriosis (n = 20)</th>
<th>Laparoscopy negative abdominal pain (n = 20)</th>
<th>Irritable bowel syndrome (IBS) (n = 20)</th>
<th>Comparison of groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (range)</td>
<td>35.2 (23–66)</td>
<td>31.1 (19–68)</td>
<td>36.0 (22–47)</td>
<td>35.0 (22–48)</td>
<td>34.3 (20–54)</td>
<td>p=0.037</td>
</tr>
<tr>
<td>Rome positive (n)</td>
<td>0</td>
<td>13*</td>
<td>11*</td>
<td>17*</td>
<td>20*</td>
<td>p=0.001</td>
</tr>
<tr>
<td>IBS-D</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>IBS-C</td>
<td>0</td>
<td>6</td>
<td>5</td>
<td>11</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>IBS-mixed</td>
<td>0</td>
<td>4</td>
<td>1</td>
<td>4</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>IBS-U</td>
<td>0</td>
<td>2</td>
<td>5</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Anxiety score, mean (range)</td>
<td>6.0 (1–17)</td>
<td>8.5 (4–14)†</td>
<td>7.5 (1–15)</td>
<td>8.0 (4–18)†</td>
<td>9.0 (1–15)</td>
<td>p=0.04</td>
</tr>
<tr>
<td>Depression score, mean (range)</td>
<td>3.0 (0–16)</td>
<td>4.0 (1–14)</td>
<td>3.0 (0–18)</td>
<td>5.0 (0–13)</td>
<td>4.0 (0–17)</td>
<td>p=0.13</td>
</tr>
<tr>
<td>IBS severity score, mean (range)</td>
<td>50.0 (0–149)</td>
<td>237.7 (68–423)‡</td>
<td>201.0 (60–420)‡</td>
<td>251.8 (120–420)‡</td>
<td>340.0 (207–465)‡</td>
<td>p=0.001</td>
</tr>
<tr>
<td>Quality of life score, mean (range)</td>
<td>338.3 (75–541)</td>
<td>336.4 (120–627)</td>
<td>333.9 (192–456)</td>
<td>317.1 (133–425)</td>
<td>317.8 (134–584)</td>
<td>p=0.10</td>
</tr>
</tbody>
</table>

*Comparison with controls: p<0.001.
†Comparison with controls: p<0.05.
‡Comparison with IBS: p<0.05.
Table 2  Physiological data

<table>
<thead>
<tr>
<th></th>
<th>Laparoscopy controls (n = 20)</th>
<th>Minimal to mild endometriosis (n = 28)</th>
<th>Moderate to severe endometriosis (n = 20)</th>
<th>Laparoscopy negative abdominal pain (n = 20)</th>
<th>Irritable bowel syndrome (IBS) (n = 20)</th>
<th>Comparison of groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>First sensation (mm Hg), mean (95% CI)</td>
<td>19.2 (16.3 to 22.1)</td>
<td>15.3 (14.0 to 166)</td>
<td>15.5 (13.6 to 174)</td>
<td>16.3 (14.1 to 18.5)</td>
<td>12.6 (10.8 to 14.4)*</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>Stool sensation (mm Hg), mean (95% CI)</td>
<td>32.6 (28.0 to 36.0)</td>
<td>25.9 (23.6 to 28.2)</td>
<td>26.0 (21.9 to 30.1)</td>
<td>28.0 (22.6 to 33.2)</td>
<td>24.3 (20.4 to 28.3)**</td>
<td>p = 0.027</td>
</tr>
<tr>
<td>Pain threshold (mm Hg), mean (95% CI)</td>
<td>35.9 (32.0 to 43.0)</td>
<td>28.1 (24.5 to 31.6)**</td>
<td>28.0 (24.3 to 32.6)**</td>
<td>32.7 (28.8 to 36.6)</td>
<td>25.4 (21.7 to 29.3)*</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>Static compliance, mean (95% CI)</td>
<td>6.4 (5.4 to 7.5)</td>
<td>5.6 (4.4 to 6.8)</td>
<td>7.2 (5.7 to 8.8)</td>
<td>8.1 (6.0 to 11.2)</td>
<td>8.3 (6.5 to 10.0)</td>
<td>p = 0.18</td>
</tr>
<tr>
<td>Dynamic compliance, mean (95% CI)</td>
<td>7.1 (5.7 to 8.6)</td>
<td>7.1 (5.9 to 8.2)</td>
<td>8.4 (7.3 to 9.6)</td>
<td>8.3 (6.2 to 10.4)</td>
<td>9.1 (7.8 to 10.5)</td>
<td>p = 0.18</td>
</tr>
</tbody>
</table>

Comparison with controls: *p < 0.001, **p < 0.05, ***p < 0.01, ****p < 0.001.

Hyperesthesia is common in patients with this condition and may be significantly contributing to their symptoms. This finding could therefore have major implications with regard to the treatment of endometriosis.

In the laparoscopically normal healthy volunteers visceral sensory thresholds were within normal limits whereas the patients with IBS, as might be anticipated, showed visceral hyperesthesia. It would be expected that at least a proportion of patients with laparoscopically normal abdominal pain might actually have IBS, and this was suggested by the fact that 70% fulfilled the Rome III criteria for the condition. Consequently, this group also had sensory thresholds that did not differ significantly from those of the individuals with IBS. Irrespective of the extent of their disease, the patients with endometriosis also exhibited visceral sensitivity in the range seen in patients with IBS, although it should be noted that the prevalence of constipation was somewhat higher in patients with IBS than in those with endometriosis so they were not exactly comparable. However, the most notable finding was that there was a highly significant difference in thresholds for pain between the patients with endometriosis and controls, the patients with endometriosis exhibiting hyperesthesia. Furthermore, the proportion of these patients who exhibited visceral hyperesthesia was 60% and 35% for minimal to mild endometriosis and moderate to severe endometriosis, respectively, and this is similar to that reported in the literature for IBS and what was observed in the patients with IBS included in this study. The thresholds for first sensation and stool sensation showed a similar trend to that for pain but did not reach significance, which is not unusual in studies of this type. Moreover, the first sensation and stool sensation thresholds are not considered to be as discriminatory as the pain threshold and therefore are not even subjected to tracking in the testing procedure. It is also of interest to note that there were no differences in the endometriosis pain scores between those with minimal to mild disease and the more severely affected individuals. This is entirely consistent with the literature as well as clinical experience, and again serves to emphasise the problem of the relationship between symptomatology and extent of disease in this condition.

The observation that laparoscopy did not appear to result in increased visceral sensitivity in the healthy volunteers makes the possibility that this procedure might be the cause of this abnormality in the other groups highly unlikely. However, there are at least two other possible explanations for the hypersensitivity seen in the patients with endometriosis. First, it may be that endometriosis of any extent might sensitise the contents of the peritoneal cavity including the gut in some way or, alternatively, that these patients actually had a generalised visceral hyperesthesia associated with IBS, especially as so many of these patients with endometriosis fulfilled the Rome criteria for IBS. To our knowledge, there are no data on whether endometriosis can sensitise the peritoneal cavity, although our observations that patients with Rome-negative endometriosis with more severe disease were significantly less sensitive than Rome-positive individuals suggest that endometriosis on its own does not lead to rectal sensitisation. In addition, it is not known whether patients with IBS with rectal hyperesthesia have increased sensitivity which extends to the peritoneum. However, it has been shown that the hyperesthesia in patients with IBS is not confined to the rectum and can affect the whole gastrointestinal system. Furthermore, hyperesthesia beyond the confines of the gut in IBS is suggested by the findings of auditory and visual hyperesthesia in these individuals and the coexistence of other syndromes such as fibromyalgia. Furthermore, it is noteworthy that these patients frequently also have bladder symptoms and, on testing, have been shown to have urodynamic abnormalities, which again emphasises the diffuse nature of IBS. There is therefore some evidence to suggest that IBS is associated with hyperesthesia extending beyond the confines of the gut, which supports the notion that patients with such a generalised hyperesthesia may be more likely to report symptoms from an inflamed area, wherever that might be. Therefore, in an individual with generalised hyperesthesia, if they have an

![Figure 1](https://example.com/image1.png)
inflammatory process in both the peritoneal cavity (endometriosis) and the gastrointestinal mucosa (IBS), they may well report symptoms from both anatomical sites. This makes it somewhat less likely that our observations represent a coincidental finding of endometriosis in patients with IBS seeking healthcare, although this remains a possibility which would still have profound implications with regard to treatment, especially in individuals with minimal disease.

The role of inflammation in endometriosis and IBS is a further aspect that merits discussion. Ever since Chaudhary and Truelove first described the occurrence of IBS following a dysenteric infection, evidence has continued to emerge suggesting that there might be a persistent low-grade inflammatory response within the gastrointestinal mucosa of at least some cases. It is therefore noteworthy that there has been an increasing amount of attention on inflammation in relation to endometriosis, and in some instances the research on inflammation in IBS almost completely mirrors that which is being undertaken in endometriosis. For example, there have been reports of mast cell activation in both conditions and that these activated mast cells are in close proximity to nerve fibres and also that T-cell receptors may also be involved in the inflammatory process. Thus, the evaluation of various inflammatory markers in lапoscopy obtained seminal biopsies in these patients with visceral hypersensitivity would be of considerable interest, but was obviously beyond the scope of this study.

Whatever the cause of the visceral hypersensitivity identified in these patients with endometriosis, it may open up new treatment options especially in those with severe symptoms despite apparently mild disease. Although it is now recognised that IBS is a multifactorial disorder, visceral hypersensitivity is thought to be a sufficiently important contributing feature that it is viewed as a logical target for pharmacological intervention. As a consequence, drugs that could possibly have an effect on this pathophysiological parameter such as pregabalin and ketotifen are being assessed, and it is thought that the tricyclic antidepressants, which are often very effective in IBS, at least partly mediate their benefit by reducing the sensitivity of the gut. Consequently, in patients with mild endometriosis, a trial of one of these modulators of visceral sensitivity may be worthy of consideration before embarking on more aggressive treatment, particularly surgery. Obviously, the situation is far more complicated in the more severe forms of the disease but, even in these patients, attempts to reduce hypersensitivity in conjunction with other forms of treatment might be a viable option. The question of whether the use of desensitising agents should be undertaken empirically or only after sensitivity testing would need to be answered by further research. In addition, it would be advisable to treat any symptoms of IBS, especially if the patient meets the criteria for this condition and their complaints seem out of proportion to the laparoscopic findings.

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Patient consent: Obtained.

Ethics approval: The study was approved by the South Manchester Research Committee and all participants gave written informed consent.

Contributors: Original hypothesis PJS; design and supervision of the study: PJS, SH, TSO; conduct of the study: BS, CS and AA; analysis of data: JM; writing and revision of the paper: all authors.

Provenance and peer review: Not commissioned, externally peer reviewed.

REFERENCES


8.8 ABDOMINAL BLOATING AND DISTENSION: WHAT IS THE ROLE OF THE MICROBIOTA (APPENDIX)
Abdominal Bloating and Distension: What Is the Role of the Microbiota

B. Issa · N. A. Wafaei · P. J. Whorwell

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Abstract Most patients with irritable bowel syndrome complain of a sensation of an increase in pressure within their abdomen during the course of the day which is called bloating and, in approximately half of these individuals, this symptom is accompanied by an actual increase in abdominal girth, which is referred to as distension. The pathophysiology of these two phenomena is somewhat different and it is now recognised that a whole variety of overlapping mechanisms are involved. Some of these are potentially amenable to treatment by modification of the bacterial flora of the gut and this article reviews the evidence for this.

Keywords Irritable bowel syndrome · Bloating · Distension · Microbiome

Background

Patients with functional gastrointestinal disorders, especially irritable bowel syndrome (IBS), frequently complain of bloating and distension and it is not uncommon for them to report that these features often occur on a daily basis and, as a consequence, are especially bothersome. Another problem is that their management has always proved challenging, probably because, until recently, their pathophysiology has been poorly understood. However, the situation is now beginning to change with the recognition that a whole variety of factors may be involved and, importantly, that bloating and distension should be regarded as different but overlapping conditions. It is now suggested that the term bloating should be applied to the sensation of an increased pressure within the abdomen and that the term distension should only be used when this sensation is accompanied by an actual increase in abdominal girth. Recent research has indicated that in approximately 50% of patients reporting bloating, this sensation is accompanied by distension [1] and that there are subtle differences in the mechanisms underlying these conditions [2, 3].

Putative Causes of Bloating and Distension

Research on bloating and distension has been hampered by the lack of availability of suitable methods of investigation but this has been changed by the advent of techniques such as the gas challenge technique [4, 5], abdominal inductance plethysmography [6, 7], abdominal and diaphragmatic electromyography [8, 9], CT scanning [10], and no doubt magnetic resonance imaging will contribute in the future. The application of such methodology has resulted in the recognition that bloating tends to be associated with a phenotype characterised by increased visceral sensitivity [11], impaired gas handling [4], and diarrhoea [12], whereas distension is more often related to constipation [12], delayed gastrointestinal transit [12], weak abdominal musculature [13], and an abnormal accommodation reflex.
where there is paradoxical contraction of diaphragmatic and abdominal muscles in response to an increase in abdominal pressure. In addition, there is evidence that in at least a proportion of patients with IBS, the bacterial flora of the gut may be disturbed [14–16] and additionally, fermentation may also contribute to symptoms [17] raising the possibility that these two factors may also contribute to both bloating and distension.

**Treatment Approaches to Bloating and Distension**

As a consequence of this evidence that bloating and distension differ mechanistically to some extent, it follows that the success of treatment is likely to be enhanced if the appropriate pathophysiological abnormality is targeted in a particular individual. For example, relieving constipation is more likely to improve distension whereas for a patient with bloating alone, aiming to reduce visceral hypersensitivity is a more logical strategy. Unfortunately, the situation is somewhat complicated by the fact that, at least in the UK, patients tend to describe their problem as bloating, irrespective of whether they are troubled by bloating or distension, but at least these pathophysiological observations provide a framework for a systematic approach to managing these problems.

Of the various pathophysiological mechanisms involved in bloating and distension that have been enumerated above, it seems reasonable to speculate that dysbiosis, gas handling, constipation, diarrhoea, visceral hypersensitivity, and fermentation might be amenable to modification by use of probiotics or antibiotics and there follows a discussion providing some evidence to support this view.

**The Therapeutic Potential of Antibiotics and Probiotics**

The notion that the microbiota of the gastrointestinal tract may be disturbed in patients with IBS has largely been prompted by two observations. First, for some patients with IBS there seems to be evidence of a low-grade inflammatory response within their gastrointestinal mucosa. Second, for others there is evidence of small intestinal bacterial over-growth (SIBO). Given that some probiotic bacteria have been shown to have a range of anti-inflammatory activity it is not surprising that their use has been advocated as a possible treatment for IBS. A relatively large number of controlled trials have been reported to date and, although their design has been rather variable, most have shown some evidence of a positive effect [18]. However, it should also be noted that different symptoms seem to respond to different probiotics but in a significant proportion of studies an improvement in subjectively reported bloating has been documented. Evidence for SIBO has come from studies using breath testing techniques after carbohydrate ingestion and, depending on the substrate used, the reported prevalence of the SIBO in IBS is somewhat variable [19]. Nevertheless, these observations have led some researchers to speculate that antibiotics, especially if they are of the non-absorbable variety, might have therapeutic potential in IBS, and the first studies used neomycin with positive results [20]. Subsequently, rifaximin has become the antibiotic of choice and there is now evidence that the use of this drug over a period of 7–14 days can reduce symptoms, including gaseousness and bloating, not only in the short term but also for a period of up to 3 months [21–23]. Obviously, the prolonged use of antibiotics to treat a condition such as IBS could not be advocated, but if a short course of a non-absorbable antibiotic is beneficial with a substantial carry over effect, then this option might well have some utility. One of the problems with any research in this area has been that, until recently, evidence of the role of bacteria in conditions such as IBS has been hampered by the fact that it could only be investigated indirectly by the use of techniques such as breath testing, or directly by culture techniques which are impeded by the fact that only a relatively small proportion of the gut microbiota can be cultured [19, 24, 25]. However, with the advent of molecular techniques, it is now possible to more accurately address this issue, and, after use of such approaches, reports are already emerging of variations in the microbiological profiles of gut bacteria in IBS [16, 26–32].

**Specific Evidence of the Benefit of Individual Antibiotics or Probiotics in Bloating and Distension**

Over the years, the Barcelona group have undertaken a series of elegant studies showing that compared with controls, patients with IBS have impaired handling of a gas load leading to gas trapping and the symptom of bloating [4]. This observation suggests that first, patients with bloating should avoid carbonated drinks and foods that tend to produce gas, and, second, that an attempt to alter endogenous gas production by modification of the bacterial flora is worthy of consideration, and that this could possibly be achieved by the use of an antibiotic or a probiotic. Certainly, some of the studies using rifaximin (Fig. 1) have supported this view [21–23, 33] and it is noteworthy that a reduction in bloating has been reported after use of some probiotics, for example VSL#3 [34, 35] and *Bifidobacterium infantis* 35624 [36], although whether this is a result of a reduction of endogenous gas-forming organisms has to be speculative and an alternative explanation might be an effect on visceral sensation.
Visceral hypersensitivity is one of the most well described pathophysiological abnormalities in IBS [37, 38] and it has even been suggested that it might be a biological marker for the condition [39]. Consequently, it is frequently regarded as a potential target for treatment, especially by the pharmaceutical industry. The mechanism by which sensitisation is induced is not clear but it is of note that many patients date the onset of their IBS to an episode of gastroenteritis [40, 41]. It has been suggested that this could lead to sensitisation of the gastrointestinal mucosa as a result of persisting, low grade, inflammation or, alternatively, by a change in the gastrointestinal flora. It is, therefore, not surprising that it has been suggested that probiotics might have utility in reducing visceral sensitivity. To our knowledge there have, so far, been no studies of this in humans but there are promising data in animals [42–44] indicating that it is certainly worthy of further exploration.

Constipation [1] and delayed gastrointestinal transit [12] are associated with distension and it seems reasonable to suppose that improving constipation and hastening transit might lead to improvement of this problem. Consequently, it is of interest that the Barcelona group have shown that accelerating the transit of gas through the gut by administration of a prokinetic agent such as neostigmine can reduce girth [45]. Thus, if transit could be hastened by administration of a probiotic this could be an approach that might have potential in relation to reduction of abdominal distension. In physiological studies DN-173-010 has been shown to accelerate gastrointestinal transit [46–49] and, in clinical trials, to reduce the subjective reporting of bloating [37]. Therefore, this organism should, theoretically, have the potential to improve distension and this question has recently been addressed in a study using abdominal inductance plethysmography to objectively measure abdominal girth in patients with constipation-predominant IBS. Compared with a matching placebo, the active probiotic, delivered as a yogurt twice daily, significantly reduced abdominal girth (Fig. 2), and this was accompanied by an acceleration in both small and large bowel transit and an improvement in symptoms [50]. It is also noteworthy that in an unrelated study, the frequency of the migrating motor complex was found to decrease in patients with IBS in whom the presence of SIBO was suggested by an abnormal lactulose breath test [51]. Interestingly, motility seemed to be enhanced once this overgrowth had been eradicated [51].

**Conclusion**

It seems that some probiotics and antibiotics may have a role in treating bloating and distension and this is possibly as a result of an effect on some of the mechanisms involved in the pathophysiology of these two common features of functional bowel disorders. Furthermore, it could be expected that as our understanding of the gastrointestinal microbiota and bloating and distension improves, even better control of these enigmatic symptoms might be forthcoming.

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References


