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Chapter 9

Functional Gastrointestinal Symptoms in Women with Pelvic Endometriosis

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http://dx.doi.org/10.5772/56611

1. Introduction

Gastrointestinal symptoms are frequently encountered in women diagnosed with endometriosis. Women with endometriosis appear to complain more commonly of gastrointestinal symptoms such as gastro-oesophageal reflux and dyspepsia. The psychological profile of patients with endometriosis may promote these symptoms. As a reaction to high levels of perceived stress, neuroendocrine-immune imbalance has been demonstrated in women diagnosed with endometriosis. Pharmacological agents used to treat psychological dysfunction, and symptoms of endometriosis such as dysmenorrhoea, may lead to undesirable gastrointestinal symptoms.

Through neuroendocrine and immunological intermediaries, the gastrointestinal system may also interact with the physiology of the female genital system. These variables have directed some workers to suggest an interrelationship between both systems including the occurrence of pathology. Gastrointestinal symptoms may act as a guide to dietary modification which may result in improvement in the symptomatology of endometriosis.

2. Epidemiology of gastrointestinal symptoms and endometriosis

It is becoming apparent that although anatomically separate, gastrointestinal symptoms do overlap with pelvic endometriosis. Endometriosis is the occurrence of endometrial tissue outside the uterus. Endometriotic deposits are mainly found on the ovaries, utero-sacral ligaments and pelvic peritoneum. Endometriosis affects one fourth of young women under the age of 30 years with an overall incidence of 7% to 10 % of women. Subfertility has been noted in 20-50% of women found to have endometriosis while more than 80% of women

complaining of chronic pelvic pain have been diagnosed as having this condition. Conversely endometriosis has been diagnosed in 20-50% of women who were completely asymptomatic, unaware that they had this pelvic pathology [1].

Gastrointestinal symptoms appear more prevalent in women diagnosed with pelvic endometriosis [2,3,]. Specific signs and symptoms result in frequent medical consultation are associated with presence of endometriosis [4]. The anatomical separation between the gastrointestinal tract and the female genital tract may prima facie, appear disparate without any anatomical or physiological association. In a study by Muscat Baron et al [5,6] however, gastrointestinal symptoms such as heartburn and dyspepsia were significantly more commonly found in women with endometriosis as compared to a control group. This was a prospective trial involving 57 menstrual women who had undergone laparoscopic examination of the pelvis for a diverse number of abdominal and gynaecological symptoms. The women recruited to the study were asked a comprehensive questionnaire which included information on gastrointestinal symptoms, gynaecological symptoms, dietary intolerance and general symptoms. During laparoscopy 23 women were diagnosed as having pelvic endometriosis while in the other thirty-four this diagnosis was excluded. Upper gastrointestinal symptoms such as heartburn and dyspepsia were found more commonly in the endometriosis group reaching statistical significance ($p < 0.001$). These results posed the enquiry as to why two apparently anatomically distant systems, that is the gastrointestinal tract and the female reproductive system, should influence each other [5,6].

Women diagnosed with endometriosis have been shown to have concomitant irritable bowel syndrome symptoms. Ballard et al have shown that women with pelvic endometriosis were also diagnosed with irritable bowel syndrome (OR 1.6 [95% CI: 1.3-1.8]) [4]. Lower gastrointestinal symptoms in the form of diarrhoea and loose stools have been found more commonly found in women diagnosed with endometriosis. As opposed to the upper gastro-intestinal tract, both the small and to a greater extent the large bowel is in close proximity with the female genital tract. Both systems (intestinal and reproductive) throughout their physiological functioning are likely to influence each other [5,6].

It must be kept in mind that gastrointestinal symptoms commonly occur in the general population. Although estimates vary according to the diagnostic criteria used, 10–40% of the adult population experience heartburn and dyspepsia in Western countries. Gastro-oesophageal reflux disease increases with age, rising sharply beyond the fourth decade. More than half of the patients effected are aged between 45 and 64[7].

Dyspepsia also affects between 20% and 40% of the Western populations. A quarter of all cases of dyspepsia are though to be related to gastric and duodenal ulcers [8]. Several studies from the 1940's to the 1980's reported that population prevalence of 18%[9], 26%[10] and 31% [11] of people referred with dyspepsia were found to have peptic ulcers. Recently this percentage has fallen to around 10–15%[7]. Although mortality in people with gastrointestinal disorders is not raised compared with the general population, these disorders have a significant impact on quality of life. It has been shown that 75% of people with heartburn and dyspepsia suffered persistent symptoms and impaired quality of life over periods of 10 years or more; 30–50% never returned to work and were unable to carry out household tasks [12].

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3. Pathogenesis of endometriosis and gastrointestinal symptoms

The enigmatic pathogenesis of endometriosis has led to the formulation of several hypotheses, but none have been proven conclusively. The elusiveness of its pathology has directed some workers to search beyond the female genital tract and concentrate their efforts at the gastrointestinal system, the small and large bowel being in close anatomical proximity to the female genital tract (Figure 1.)[5,6,13]. The overlap of symptoms between both the gastrointestinal pathology and endometriosis influences clinical practice and in several women leads to delayed or misdiagnosis (Figure 1.).

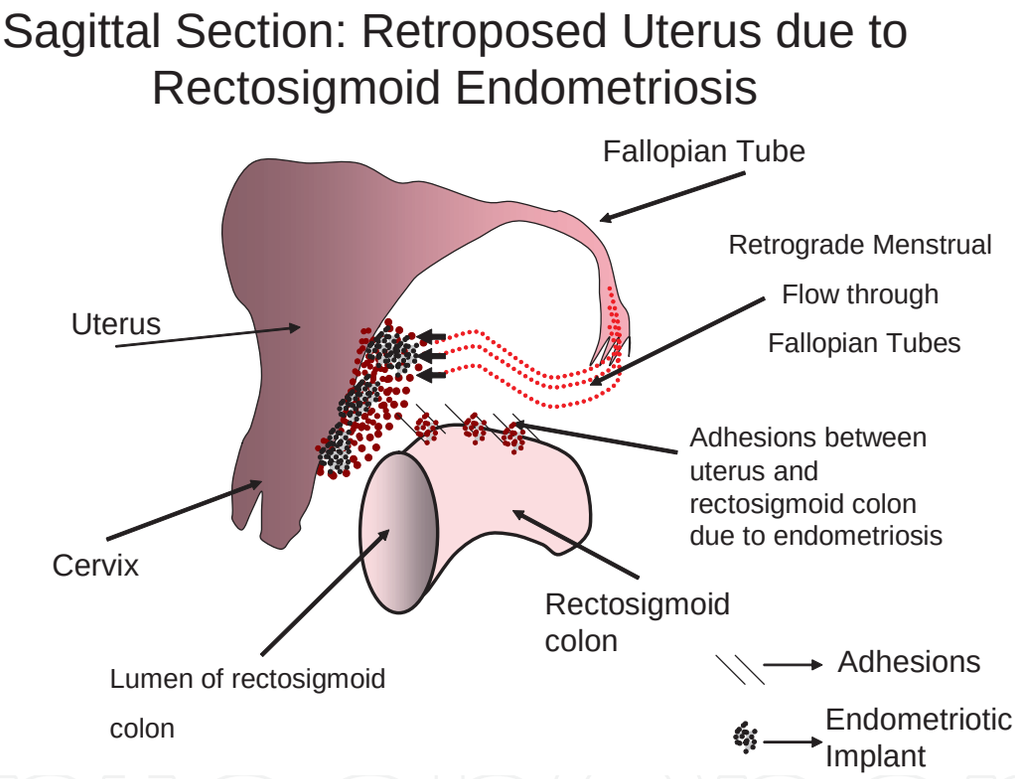

Figure 1. Following retrograde menstrual flow through the Fallopian tubes, endrometriotic deposits colonize adjacent peritoneal structures. The peritoneal structures involved include ovaries, utero-sacral ligaments and adjacent bowel especially the rectosigmoid colon. Following endometriotic deposition adhesion formation results. This may lead to a retroverted uterus due to endometriosis-included adhesions between rectosigmoid colon and posterior aspect of uterus, with obliteration of the Pouch of Douglas.

Physiological studies indicate that gastric emptying does not appear to be affected by the menstrual cycle. Abdominal symptoms related to the upper gastrointestinal tract appear more commonly during the follicular phase. During the follicular phase the transit time in the small bowel is longer. The normal menstrual cycle has no effect on gastric motility suggesting that gastric emptying does not change significantly between the follicular and luteal phases [14]. Almost 50% of women with irritable bowel syndrome report a perimenstrual increase in symptoms [15].

4. Psychological background to the co-existence of endometriosis and gastrointestinal symptoms

Emotional and mood disorders in women have been significantly detected in women suffering from endometriosis. These disorders were found more commonly in women with endometriosis (11/23 $p < 0.03$), admitting regular administration of anxiolytic and/or anti depressant therapy for symptoms related to significant anxiety or depression [5].

In a prospective study by [16], out of 104 women diagnosed with pelvic endometriosis 87.5% of women complained of anxiety. This anxiety state was mild in 24% and severe in 63.5% of the subjects studied. Correlations between pain intensity and anxiety symptoms, were also obtained using the State-Trait Anxiety Inventory (STAI) (state, P=0.009; trait, P=0.048) and the Hamilton Rating Scale for Anxiety (HAMA) (P=0.0001). Moreover anxiolytic treatment with benzodiazepines such as clonazepam has been used in women with endometriosis. A number of these subjects also required prolonged treatment with serotonin selective serotonin reuptake inhibitors (SSRI's) [16].

Depression has also been noted to be prevalent in women with pelvic endometriosis, a high proportion of which require anti-depressant therapy. Depressive symptoms were observed in 86.5% of patients with pelvic endometriosis (mild in 22.1%, moderate in 31.7%, and severe in 32.7%) [16]. In a similar percentage (86%) of women, depression was detected in the women with endometriosis complaining of chronic pelvic pain [17]. Work inhibition, dissatisfaction, and sadness, were observed at a significantly higher rates in the group with abdominal pain [17]

The above mentioned psychological profile of these women may have been moulded from a very young age. The cyclical experience of the symptoms of severe dysmenorrhoea and menstrual disorders from puberty, may have conditioned these women to acquire certain personality traits as a reaction to the cyclical physical and subsequent psychological suffering they sustained [16]. Lower quality of life indices correlated with high pain scores. Lower quality of life status in psychological and environmental perspectives resulted in an inverse relationship between pain scores and the psychological dimension of quality of life ($r = -0.310$, $P = .02$)[18].

Mood disorders in adult women with endometriosis are associated with co-morbidities such as pain syndromes including irritable bowel syndrome, vulvodynia, fibromyalgia and asthma have been noted with in adult women with endometriosis. These co-morbidities appear to have their conception early in reproductive life in adolescents and young women. A study by Smorgick et al (2013) reviewing 138 adolescents/young women (younger than 24 years) demonstrated a prevalence of comorbid pain syndromes 56% women, mood conditions in 66 (48%) women, and asthma in 31 (26%) women [19].

Exacerbations of gastrointestinal motility disorders such as gastro-oesophageal reflux and irritable bowel syndrome are associated with the emergence of psychosocial stressors. Naliboff et al [20] assessed 60 subjects with current heartburn symptoms and correlated for the occurrence of stressful life events retrospectively over the preceding 6 months and prospec-

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tively for 4 months. The occurrence of a severe, sustained life stress during the previous 6 months significantly predicted increased heartburn symptoms during the following 4 months. Anxiety showed the strongest correlation to impaired quality of life and depression to heartburn medication use. Similar to other chronic conditions such as irritable bowel syndrome, heartburn severity appears to be most responsive to major life events. Both heartburn and irritable bowel syndrome may be related to gastrointestinal motility disorders[20]. In the upper gastrointestinal tract oesophageal acid exposure due to inhibition of gastric emptying of acid may lead to heartburn. Alternatively motility disorders affecting the lower intestinal tract lead to irritable bowel syndrome.

On further investigation of gynaecological complaints, once the diagnosis of endometriosis is established, the phobia of infertility may set in, further compounding the psychological profile. If infertility does occur in these women, then depressive symptoms are more likely to appear. Self-reported depression was more common in subfertile women (n = 1,031), with endometriosis (O.R. 5.43, C.I. 4.01-7.36) compared with fertile women (n = 4,905) [21].

5. Neuro-endocrine imbalance in association with Gastrointestinal symptoms and Endometriosis

The majority of women suffering from endometriosis are well versed in their condition. With easy access to medical literature, besides subfertility, the risk of inflammatory bowel disease and ovarian cancer has now become universally known to most women suffering from endometriosis [21]. All these factors exacerbate the tenuous emotional status of these women (Figure 2.)

In response to high levels of perceived stress, neuroendocrine-immune imbalance has been alluded to as a reaction to the symptoms of endometriosis. Serum prolactin levels were significantly higher in infertile women with stage III-IV endometriosis (28.9 +/- 2.1 ng/mL) than in healthy controls (13.2 +/- 2.1 ng/mL)[22]. Elevated serum cortisol levels were noted in infertile women with stage III-IV endometriosis (20.1 +/- 1.3 ng/mL) compared to controls (10.5 +/- 1.4 ng/mL) [22]. Perception of stress has been noted to trigger or intensify the incidence or exacerbation of diseases such as inflammatory bowel disease, immunological cutaneous conditions, or pregnancy complications such as spontaneous miscarriage and pre-eclampsia. The effect on the immunity of the intestinal mucosa by stress has been implicated as a potential mechanism leading to irritable bowel syndrome. This is thought to be mediated through altered function of the hypothalamic-pituitary-adrenal axis and the sympathetic nervous system. Both of these systems can modulate mucosal immune function. A study by Chang et al indicated that basal adrenocorticotropin hormone levels were significantly blunted ($P < 0.05$), while basal and stimulated plasma cortisol levels were higher in patients with irritable bowel syndrome. Patients with irritable bowel syndrome presenting with diarrhoea had significantly decreased mRNA expression of mucosal cytokines [interleukin (IL)-2, IL-6] in the sigmoid colon versus controls ($P < 0.05$) [24].

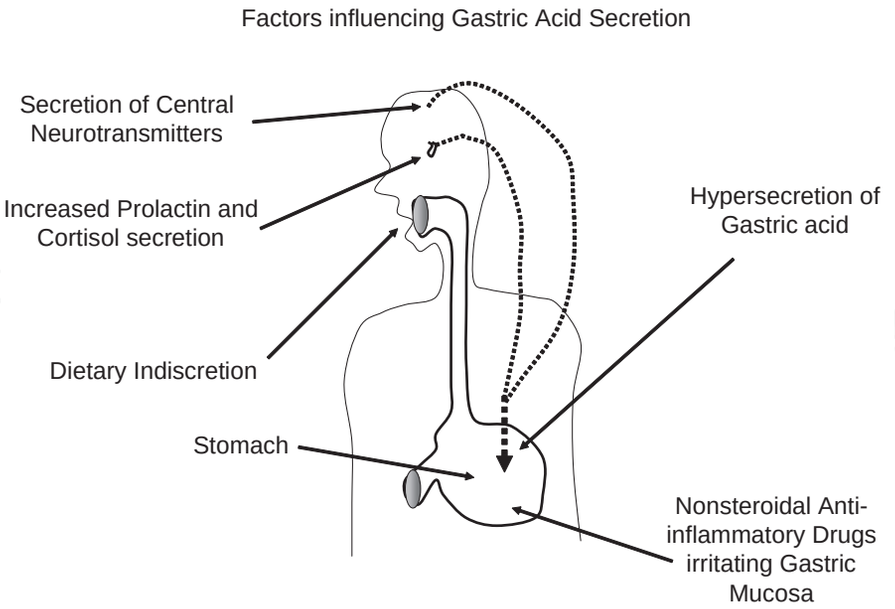

Figure 2. The secretion of central neurotransmitters and hormones such as cortisol and prolactin increase the secretion of gastric acid. This compounded by dietary indiscretion and injudicious ingestion of nonsteroidal inflammatory agents increase risk for gastric mucosal ulceration.

The association between psychological status and the gastrointestinal tract is well established. Dr William Beaumont in 1833 demonstrated the influence of psychological stress on gastric mucosal changes. Acclaimed as the Father of Gastric Physiology, Dr Beaumont carried out observations and experiments on an individual known as Alexis St Martin. St Martin had sustained a gastric fistula followed gunshot wound to the stomach, exposing a sliver of gastric mucosa. Beaumont observed that the exposed gastric mucosa instantly reddened when St Martin was angered, connecting the neuroendocrine-emotional status with gastric physiology [25].

Heartburn and dyspepsia are acknowledged symptoms related with psychological and mood disorders. Gastro-oesophageal reflux disease can be anatomically traced back to dysfunction of the gastro-oesophageal junction, however psychological factors can play an important role in the exacerbation of heart-burn. Well defined personality factors modulate the effect of stress on the gastro-oesophageal junction, just as they can influence the perception and assessment of symptoms. Gastric and small intestinal motor disorders and stomach acid hypersecretion, interact with psychological and neurohormonal resulting in the pathogenesis of dyspepsia. Greater proximal extension of acid during reflux episodes has been demonstrated in patients with proven gastro-oesophageal reflux disease. These patients describe a shorter history of symptom onset and worse anxiety scores. Endoscopic investigation depict findings compatible with gastritis [26].

Altered secretion of gastric acid in the stomach has been linked with a vast array of modulators supporting the neuro-endocrinological connection. Central neurotransmitters and/or neuromodulators may excite or inhibit gastric acid secretion. Excitatory neuro-endocrine modulators such as gamma-aminobutyric acid (GABA), acetylcholine, thyrotropin releasing hormone,

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oxytocin have been cited. On the contrary, noradrenaline, adenosine, bombesin, calcitonin-gene related peptide, corticotropin releasing factor, beta-endorphin, neurotensin, neuropeptide Y, insulin-like growth factor II and prostaglandins have been shown to inhibit gastric acid secretion.

Several of these neuro-endocrine mediators have also been noted in endometriosis. Deep infiltrating endometriosis is associated with severe and frequent chronic pelvic pain. In these cases significantly more nerve fibres are detected histologically, than in superficial peritoneal endometriotic lesions. Deep infiltrating endometriotic lesions were shown to be innervated abundantly by sensory nerve fibres utilizing acetylcholine and norepinephrine as neurotransmitters [27]. Women with endometriosis have been noted to have lower levels of progesterone in serum in the follicular phase and progesterone levels were inversely correlated to pain scores. Progesterone receptor positive peritoneal lymphocytes of CD56(+) and CD8(+) type were increasing found in advanced endometriosis. Cytokine secretion by peritoneal cells, was higher in cells derived from endometriosis patients and could be further heightened by corticotrophin releasing hormone mediated inflammation. Peripheral corticotrophin releasing hormone increasing with anxiety and emotional stress, might contribute to the peritoneal inflammation present in endometriosis [28,29].

6. Gastrointestinal symptoms, the menstrual cycle and endometriosis

An increase in the prevalence of gastro-intestimal symptoms are noted around the time of menses and early menopause [30]. These are periods in the reproductive cycle whereby a significant decline or low level of ovarian hormones in serum are noted. These observations suggest that estrogen and progesterone withdrawal may contribute either directly or indirectly to the occurrence of gastrointestinal symptoms and possibly to pathology [30].

Due to significant overlap between the symptoms of endometriosis and symptoms related to endometriotic deposits on the gastrointestinal system, endometriosis has been referred to the great masquerader. Moreover the menstrual cycle may also impact on gastrointestinal function. As confirmed in the general literature, the presence of frequent menstruation in our study in patients with endometriosis increased the likelihood of related gastrointestinal symptoms.

Abdominal symptoms are significantly more pronounced at the beginning of the menstrual cycle in the follicular phase [14]. Around 30% of otherwise asymptomatic women may experience gastrointestinal symptoms at the time of menstruation, and almost fifty percent of women with irritable bowel syndrome complain of a perimenstrual increase in symptoms. Nausea, epigastric pain, and loose stools diarrhoea are more prevalent at the time of menses in women complaining of bowel dysfunction. Patients complaining of bowel motility symptoms indicate that stomach pain was higher throughout the menstrual cycle. Patients with endometriosis complained of cramping pain more commonly in the perimenstrual phase [31].

Intestinal motility disorders may be associated with the genesis of endometriosis and conversely endometriosis may influence intestinal motility. Preclinical studies have shown

significantly more colonic damage, myeloperoxidase activity, and leucocyte count numbers than controls did. Increased tension in the longitudinal muscle correlated with leuccytosis and colonic damage. Mabrouk et al have shown that in deep infiltrating endometriosis, internal anal sphincter tone was increased in 20 of 25 patients. Responses to a defaecatory function questionnaire, indicated that incomplete evacuation was the most common symptom [32].

Premenstrual symptoms may be affected by dietary components. Soy products have not been shown to alter Moos Menstrual Distress scores significantly during premenstrual phase [33]. However the ingestion of total saturated and monounsaturated fats were significantly correlated with change in Moos Menstrual Distress scores which assesses a number of premenstrual and menstrual symptomatology and subscale 'pain' in the premenstrual phase after controlling for the covariates. The consumption of cereals/potatoes/starches was significantly inversely correlated with a change in total Moos Menstrual Distress scores in the premenstrual phase [33].

Presumably due to hormonal and menstrual differences twice as many women as men seek health services for irritable bowel syndrome as men. The presence of dyspepsia in women, was found to be a significant independent risk factor for new-onset irritable bowel syndrome ([OR] = 2.14; 95% CI, 1.56–2.94). The majority of women with irritable bowel syndrome requesting medical consultation are of reproductive age experiencing the hormonal fluctuations of the menstrual cycle. However, after the age of 50 most population surveys have reported a decline in the prevalence of irritable bowel syndrome[34]. Both oestrogen and progesterone influence 5-hydroxytryptamine, an amine which is known to effect intestinal motor-sensory function. During menstruation where oestrogen and progesterone levels reach their lowest levels in the menstrual cycle, the platelet-depleted plasma concentration of 5-hydroxytryptamine in irritable bowel syndrome patients with diarrhoea were similar to healthy controls [35]. Compared to males, females with irritable bowel syndrome more commonly display non-painful gastrointestinal symptoms, constipation and somatic discomfort. There appear to be different gender-related pathways in sympathetic nervous system responses to rectosigmoid stimulation. In a study by Chang et al 58 patients with irritable bowel syndrome underwent barostat-assisted distensions of the rectum and sigmoid colon. Women with irritable bowel syndrome had significantly lower rectal discomfort thresholds compared with men with irritable bowel syndrome and healthy women who were the least sensitive. There were no significant differences in rectal discomfort thresholds between men with irritable bowel syndrome and healthy men. In both irritable bowel syndrome and control groups, women demonstrated significantly lower discomfort thresholds after noxious sigmoid stimulation ($P<0.01$) compared to men. [36].

Oral contraception results in relatively strict regulation of the menstrual cycle. Moreover the use of oral contraception is associated with reduced menstrual loss and diminished levels of dysmenorrhoea. During menstruation, women with irritable bowel syndrome using oral contraceptives complain of less cognitive, anxiety, and depression symptoms ($p < 0.05$) but no differences were seen for most symptoms of irritable bowel syndrome [37]. There may be a differential effect of oral contraception depending on gastrointestinal symptom pattern.

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The presentation of endometriosis may mimic that of inflammatory bowel disease. Cramping pain of dysmenorrhea is due to contraction of uterine smooth muscle under the influence of prostaglandins, released by the endometrium during menstruation. The inflammatory process in active inflammatory bowel disease is intimately related to prostaglandin levels. Elevated prostaglandin levels increase contractility of intestinal smooth muscle resulting in diarrhoea and abdominal pain.

There is critical importance in the clinical distinction between the diagnosis of endometriosis and inflammatory bowel disease. Nonsteroidal anti-inflammatory drugs are administered to relieve the symptoms of dysmenorrhoea in the presence and absence of endometriosis. However Nonsteroidal anti-inflammatory drugs are contraindicated in inflammatory bowel disease due to the risk of exacerbation of inflammatory bowel disease.

Dietary components in relation to symptomatic Endometriosis and Gastrointestinal symptoms

Psychological stress is also related to injudicious ingestion of dietary components that may irritate the gastrointestinal tract. Somatization, state and trait anxiety and binge eating are significant predictors of coexistent gastrointestinal disorders.

Nutrition research suggests that vitamins, minerals, and other dietary components are important underpinnings of general physical and mental health. Moreover, dietary modification may even be useful in treating mood disorder by providing a more favourable risk-benefit ratio than contemporary psychotropic agents [38].

The body mass index of women who experience depression is significantly higher than controls. Meta-analyses confirm a reciprocal link between depressive states and obesity. Self-confirmed depression, and clinically diagnosed depression are strongly associated with high body mass index.

6.1. Pharmacological treatment of endometriosis and gastrointestinal symptoms

Anxiety states have been shown to result in excessive ingestion of benzodiazepines, relaxing lower oesophageal sphincter pressure and subsequently facilitating gastro-oesophageal reflux. Depression treated with clomipramine was associated with an increased risk of oesophageal reflux (OR 4.6, 95% CI 2.0-10.6) in a duration- and dose-dependent manner [39].

Moreover, depression and its therapy were found to be predictive of developing obesity. Early during the first 6 weeks of nortriptyline treatment, weight gain commences, reaching on average 1.2 kg at 12 weeks with a resultant 0.44% increase in body mass index [40].

Chronic consumption of nonsteroidal anti-inflammatory agents to counter endometriosis-induced dysmenorrhoea and menorrhagia may lead to ulceration of the gastric mucosa. The degree of nonsteroidal anti-inflammatory gastropathy may be severe enough to develop gastric and duodenal ulceration. It appears that there is sufficient evidence to indicate that administration of nonsteroidal anti-inflammatory drugs could be considerably attenuated and adverse effects, avoided if medical practitioners were persuaded to change their prescribing practices [41].

7. Conclusion

There appears to be co-existence of gastrointestinal symptoms and endometriosis. The linkage between gastrointestinal symptoms and endometriosis may be due the psychological background and neuro-endocrine mediation. Gastrointestinal symptoms have been related to both dietary indiscretion and psychological stress both of which may, for a variety of reasons, be commonly encountered in women with endometriosis. Moreover treatment of the symptoms of endometriosis may aggravate gastrointestinal symptoms.

In suspected endometriosis, meticulous consultation carefully assessing the woman's symptomatology is required to avoid delay or possibly misdiagnosis. A delay or misdiagnosis may further exacerbate the psychological background of anxiety and depression, together with the incidence of gastrointestinal symptoms. The co-existence of gastrointestinal conditions and endometriosis may require a multi-disciplinary approach to enact effective treatment.

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