Gut and Gastroenterology

REVIEW ARTICLE

Disorders of the gastrointestinal tract in menopausal women: Review

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Abstract

Most women have a series of symptoms and signs that depend on the deficiency of estrogenic stimulation in the target organs. Menopause can be approached from different physiological, psychological and social points of view, widely known. However, the pathology gastrointestinal occurs in different stages of menopause. Gastric emptying is different in women and men, intervening hormones in an important way. Achalasia, Barrett's esophagus, gastric ulcer, poor intestinal absorption syndrome to name a few pathologies are rare. Non-alcoholic fatty steatosis, hemorrhoidal disease may occur. Colon cancer can occur, playing an important role in hormone replacement therapy. The prevalence of constipation is high in postmenopausal women.

Generalities

Menopause is defined as the cessation of menses for a least 1 year and can be corroborated by laboratory analysis that confirm the depletion of ovarian hormones. This change generally occurs between the ages of 50 and 55 years and it is preceded by a period of perimenopause [1].

Various menopausal manifestations have been well defined: waves of heat, muscle joint pain, sleep disorders, alterations in mood, irritability or anxiety, sexual problems, vaginal dryness, as well as some less known manifestations such as bladder dysfunction among many others [2]. Women attribute their symptoms to a variety of factors, including hormone changes, aging, role overload, stress, health changes, and emotional changes; epidemiologic studies link symptoms to aging, endocrine, genetic, psychosocial, cultural, behavioral, and health history factors [3].

Perimenopausal and menopausal symptoms a range of gastrointestinal symptoms, also attributed to hormonal changes, that are less frequently mentioned and discussed [1]. Studies have demonstrated that estrogen and progesterone modulate the contractile function of the lower GI segments in humans and that symptoms [1] are higher when these hormones are in lower levels [4]. Research exploring the role of fluctuating ovarian hormones and the menstrual cycle's relationship to lower GI symptoms demonstrated that lower GI symptoms increase during menses, when both hormone levels are dropping [5].

Gastroesophageal

As far as is known, there is limited information regarding GI function and menopausal states. However, previous findings suggest that as women experience menopausal symptoms related to low estrogen and progesterone levels, GERD-related symptoms increase [6].

The prevalence and pattern of symptoms of gastroesophageal reflux disease (GERD) in premenopausal, perimenopausal and menopausal women have been reported. GERD was correlated with vasomotor, vaginal, genitourinary symptoms and other symptoms of menopause. The prevalence of GERD symptoms was high, 42% of perimenopausal participants and 47% of menopausal women complained of upper gastrointestinal symptoms [1].

Both estrogen and progesterone receptors are found throughout the GI tract and likely influence its motility. These hormones presumptively mediate GI motility effects by eliciting changes in nitric oxide–containing neurons in the myenteric plexus and by affecting the number and function of mast cells in GI mucosa; Considering the fluctuations of these female hormones during the menstrual cycle, pregnancy, and menopause, including the perimenopausal transition, one may

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also expect significant differences in GI motility during each of these female hormonal stages [7]. In a study by Verrengia *et al.,* with 20 premenopausal gastroparesis women not on oral contraceptive agents, nausea and early satiety seem to worsen during the luteal phase of the menstrual cycle. No cyclical differences are otherwise observed for other gastroparesis-related symptoms, such as vomiting, bloating, abdominal pain, fullness, or loss of appetite [8].

During menopause, there is a trend toward faster gastric emptying similar to men with shorter lag phases and steeper linear emptying rates. If postmenopausal women are taking Hormone replacement therapy (HRT) though, all aforementioned measures are closer to their premenopausal rates [9]. Most psychotropic drugs are administered orally and most of their absorption takes place in the small intestine. Premenopausal women have slower gastric emptying times and lower gastrointestinal blood flow, which probably reduces the degree of absorption of the drug. The distribution of medications is influenced by the relatively low body mass index, the lower volume and blood flow, and the higher body fat percentage of women. In addition, it has been reported that renal clearance are reduced in women and liver metabolism differs by sex [10]. Furthermore, women differ from men in physiological conditions that may have an impact on psychotropic medication and the dose required for efficacy and response [11].

Obesity has adverse effects on ovulation, menstrual cyclicity and oocyte development leading to clinical symptoms such as infertility and menstrual disorders. The Roux-en-Y gastric bypass (RYGB) leads to weight loss, improved insulin sensitivity and may improve ovarian function. Results indicate that some of the endocrine changes related to regulation of ovarian function occur very early after bariatric surgery [12]. Low-grade chronic inflammation in morbid obesity is associated with impaired iron metabolism. Bariatric surgery is effective in weight loss; however, it can induce specific nutritional deficiencies, such as iron, having an even greater effect in premenopausal women. Alternatively, after surgery, there is an improvement in systemic inflammation, raising questions concerning the dosages of micronutrient supplementation [13].

A study to determine if menopausal status affects gastric emptying observed that premenopausal women and postmenopausal women taking oral estrogen and progesterone had slower gastric emptying rates of liquids. Both premenopausal women and postmenopausal women taking sex hormone replacement therapy had slower emptying of solids than men but, regarding liquids, postmenopausal women not on hormone replacement emptied solids at a rate similar to that of men. There were no differences in postprandial antral motility parameters between men and premenopausal women, this should be considered when studying gastric emptying disorders that occur predominantly in premenopausal women [14].

In the Northeast China population, many factors have been reported to affect the age of menopause, and the early or late onset of menopause may be associated with many chronic health problems. Although there is limited data available on this phenomenon, observations have associated menopause age with diabetes and gastroenteritis in elderly women, but protective against chronic gastroenteritis/peptic ulcers [15].

Another study suggested a protective effect of female sex hormones to explain the male predominance in esophageal and gastric adenocarcinoma, however more evidence is needed. Additionally, the same study suggests that MHT users have a lower risk of esophageal and gastric adenocarcinoma as well as of squamous carcinoma esophageal [7].

Iron deficiency anemia is often attributed to menstrual blood loss in premenopausal women. Endoscopy revealed a clinically important lesion and yields important findings in premenopausal women with iron deficiency anemia, which should not be attributed solely to menstrual blood loss [16]. Another study comments that in premenopausal women, iron deficiency anemia is common and menstrual flow is often considered responsible, but it is not clear if these women should undergo a gastrointestinal (GI) evaluation. The data suggest that premenopausal women with iron deficiency anemia benefit from endoscopic evaluation of the upper gastrointestinal tract regardless of menstrual flow [17]. Other authors mention that premenopausal women with iron deficiency anemia are usually treated with simple iron replacement, the standard of care for postmenopausal women and men is to exclude a gastrointestinal source of bleeding. Women with gastrointestinal symptoms, fecal occult blood and / or weight loss should undergo endoscopy [18].

The reported prevalence of significant GI lesions in premenopausal women with iron deficiency anemia (IDA) ranges from 12–95%, although in most studies, the rate is lower than 50% [19]. A study has shown that gastric emptying of solid foods in normal premenopausal young women is slower than in men of the same age, even during the first 10 days of the menstrual cycle. The findings suggest that the delay is mainly due to the alteration of distal gastric motor function [20].

Few symptomatic differences have been found between premenopausal and postmenopausal women, making it unlikely that most of the gender differences observed are directly tied to the menstrual cycle [21, 22] compared the prevalence of gastrointestinal symptoms in premenopausal and postmenopausal women. These authors verified that 38% of postmenopausal women and 14% in premenopause mentioned intestinal alterations. In this same study, the use of laxatives increased from 3.4% in premenopause to 9.4% after menopause.

The use of proton pump inhibitor (PPI) drugs was a risk factor for osteoporosis and this risk increased with therapy duration in postmenopausal women in Germany. Moreover, disorders of the esophagus and gastritis/duodenitis also increased the risk of developing this chronic condition.

Overall, the natural process of menopause, should not be overlooked, and can provide another model for addressing the question of whether declining or low levels of estrogen and progesterone play a role in abdominal pain/discomfort symptoms [23]. Further studies are required to gain a better understanding of such associations [24].

Liver and biliary tract

A study focused on postmenopausal Chinese women, found that an earlier age at menarche was associated with increased prevalence of non-alcoholic fatty liver disease (NAFLD) in later life, whereas a later age at menarche was associated with reduced prevalence of NAFLD [25].

Other authors evaluated the prevalence and risk factors for NAFLD in postmenopausal women. NAFLD showed a high prevalence among postmenopausal women in general. The presence of metabolic syndrome, and abdominal obesity were risk factors for the development of NAFLD [26].

The higher incidence of NAFLD in postmenopausal women is suggested to be related to physiological alterations triggered by hypoestrogenism and changes in the body composition [27, 28].

Other studies comment that the severity of hepatic fibrosis is greater in postmenopausal women than in premenopausal women, perhaps due to the protective effects of estrogen. However, compared to previous studies of estrogen and liver fibrosis, there are no measures of serial fibrosis, adjustment for age or longitudinal observations in coinfected populations [29, 30].

In a recently published of 9 prospective cohorts of HCV-infected patients, 37% of women with acute HCV infection cleared the virus, whereas only 21% of men did so. Female sex is also a protective factor for the progression of liver fibrosis in premenopausal but not postmenopausal women with hepatitis C virus (HCV), believed to reflect the protective effect of estrogens. In an analysis of 157 women with HCV (61 premenopausal and 96 postmenopausal), postmenopausal women had higher mean fibrosis scores than premenopausal women and rates of fibrosis progression. Moreover, among postmenopausal women, there was less advanced fibrosis in those who had received hormone replacement therapy compared with those who had not and slower rate of fibrosis progression [31].

Hepatitis C virus (HCV) infection is a disease that disproportionately affects men more than women. Postmenopausal women have increased rates of fibrosis compared with women of reproductive age because they have lost the protective effects of estrogen. Estradiol and estrogen receptors in the liver protect hepatocytes from oxidative stress, inflammatory injury, and cell death, which all contribute to fibrosis. As a consequence of the overall slower liver disease progression and increased viral clearance in women, the disease burden from HCV infection is found predominantly in men. [32].

Chronic hepatitis C (CHC) and liver fibrosis progress more rapidly in men and menopausal women than in women of reproductive age. We investigated the associations among menopause, sustained virologic response (SVR), and liver damage in patients with CHC. Among women with CHC, early menopause was associated with a low likelihood of SVR, probably due to inflammatory factors that change at menopause [33].

In a previous study, the authors noted that compared to normal postmenopausal women who abstain from alcohol, it is known that estradiol levels increase statistically in normal postmenopausal women who consume alcoholic beverages moderately and these increase even more in the postmenopausal alcoholic women with cirrhosis [34].

There is increasing evidence that menopause is associated with the progression and severity of non-alcoholic fatty liver disease (NAFLD). Estrogen deficiency worsens non-alcoholic steatohepatitis (NASH) in mice models with fatty liver. The prevalence of NAFLD seems to be higher in postmenopausal compared with premenopausal women [35]. In a prospective study of postmenopausal women from Sweden, it was observed that use of HRT was associated with an increased risk of cholecystectomy [36].

Pancreas

This study refers to the fact that their results do not support a substantial association between acute pancreatitis and the use of postmenopausal hormone therapy in postmenopausal women [37].

Small intestine

During the transition to menopause, it is known that fluctuations occur in hypothalamus (gonadotropin- releasing hormone), pituitary (follicle-stimulating hormone), and ovarian hormone levels in addition to a conversion from ovarian E2 production to adrenal estrogen (estriol) production. Despite these well-established physiological changes, little is known about the impact of the menopause transition on functional bowel disorders (FBDs) including irritable bowel syndrome (IBS) [23]. Gastrointestinal symptoms are more frequent in women than in men regardless of the menstrual phase. Therefore, physicians should consider a gender-based approach in clinical practice. In addition, different symptomatic manifestations between men and women should be considered when evaluating IBS [38, 39].

Colon

The prevalence of constipation in postmenopausal women was high [40]. This symptom has been identified as a marker for cardiovascular risk factors and increased cardiovascular risk. Furthermore, because constipation is easily assessed, it may be a helpful tool to identify women with increased cardiovascular risk.

The results of a long-term prospective study of normal-weight postmenopausal women suggest that metabolically

unhealthy women have a higher risk of colorectal cancer than metabolically healthy women [41].

In this large prospective investigation of postmenopausal women, they observed statistically significant positive associations between age at menopause and age at birth of first child with risk of incident colorectal cancer after controlling for multiple other colorectal cancer risk factors [42].

The incidence of anal cancer has been increasing in the general population of women for the last few decades, but the risk of anal cancer varies considerably by risk group. Although not yet proven in formal randomized controlled trials, like cervical cancer, anal cancer may be potentially preventable through screening to detect and treat anal precancerous lesions. Given the variation in risk for anal cancer, anal squamous intraepithelial lesions (ASIL) and anal HPV infection, it is likely that an anal screening program would benefit some groups of women more than others [43].

Current or past use of menopausal hormone therapy (MHT) was associated with a modestly increased risk of (fecal incontinence) FI among postmenopausal women in the Nurses' Health Study. These results support a potential role for exogenous estrogens in the impairment of the fecal continence mechanism. [44].

Ulcerative colitis (UC) and Crohn disease are chronic inflammatory diseases with typical onset in early adulthood. These diseases, therefore, can affect a woman throughout the many stages of her life, including menstruation, sexuality, pregnancy, and menopause [45]. In a large prospective cohort of women, postmenopausal hormone therapy was associated with an increased risk of ulcerative colitis (UC) but not Crohn's disease CD. These findings indicate that pathways related to estrogens might mediate the pathogenesis of UC [46].

Others

Menopausal age may be associated with many diseases, such as diabetes, gastroenteritis, and hypertension. The results of our study also suggest that diabetes and poor mental health are correlated with menopausal age. However, after controlling for confounders, only diabetes and CGPU were found to be significantly associated with menopausal age. The association between diabetes and early menopause has been examined previously; however, results have been inconsistent. Studies conducted in both South China and Japan suggested that no association existed between menopausal age and diabetes [47, 48].

These authors suggest that endogenous estrogens may confer protection against colorectal tumorigenesis among postmenopausal women [49]. Type 2 diabetes is associated with a significantly increased risk of cancers of the liver, pancreas, colon, and rectum in postmenopausal women. The suggestion that diabetes severity further increases these cancer risks requires future studies [50-51].

Limit

One limitation is that we ł do not study gastric symptoms in different stages of menopause and ethnic groups, it is expected in future studies.

Discussion

Menopause is defined as the permanent cessation of menstruation for 12 months because of estrogen deficiency that occurs in women around an average age of 50. Until now, to the authors' knowledge, there are no published works that discuss the gastrointestinal disorders and digestive symptoms in menopause, the main focus usually being the somato-vegetative, psychological and genitourinary symptoms.

These symptoms such as, constipation and irritable bowel syndrome, can be related to the fluctuating hormone levels in a women. The fluctuation also means that the prevalence of digestive symptoms may be low or high in women. Estrogen, the female hormone, is an intestinal stimulant which during pregnancy, childbirth, menstruation and menopause, the levels of this hormone may be unbalanced, altering bowel movements.

It is advisable to know the digestive symptoms and be able to control them in time, if it were, however it is not reported that menopause is a stage in a woman's life that gastrointestinal disorders can occur.

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