

## EDITORIAL

# Menopause and the gastrointestinal system: our gut feelings

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It took decades to address the issue of physiologic differences in men and women. Even the major sex differences in the symptoms and diagnosis of cardiovascular disease were only recognized within the past 35 years.

The sex differences in the gastrointestinal (GI) system have been unexplored for an even longer time, and therefore, differences in the GI tract in women as they relate to hormonal changes have not been widely addressed.

In this issue of *Menopause*, a pilot study by Huerta-Franco et al observing gastric motility responses to stress at varying hormonal stages has brought the issue to the fore.<sup>1</sup> It has been shown that, in general, stress situations cause decreased gastric motility, and the authors aimed to differentiate gastric motility under stress at different reproductive stages, associated with respective differences in estrogen levels. They studied premenopausal, perimenopausal, and postmenopausal women under stress situations and demonstrated that premenopausal and postmenopausal women were similar to the general population, revealing a decrease in gastric motility in response to stress. The perimenopausal group, however, did not demonstrate a decrease gastric motility under stress. This very rapid physiological change to decreased estrogen levels may be an indication that many gastric changes occur in menopause, happen quickly, and can recover with time even without estrogen supplementation.

The interaction between reproductive hormones and GI function has been explored using the model of Irritable Bowel Syndrome (IBS).<sup>2</sup> Meleine and Matricon suggest that ovarian hormones may have synergistic actions with stress mediators, interact with neuromodulators, and affect gut function.<sup>2</sup> Estrogen and progesterone affect the brain–gut interactions in many complex ways, and under stress, hormones impact gut motility. Estrogen plays a role by inhibiting smooth muscle contraction, and it is known that women have slower transit times than men, in general. Higher estrogen was

associated with delayed transit times.<sup>2</sup> Thus, menopause, or the loss of estrogen, should be assumed to increase transit times. The perimenopausal women in the Huerta-Franco et al study exhibited lower basal gastric motility, which would not be expected. In response to a stress stimulus, these women, however, failed to demonstrate the decrease in gastric motility seen in both the premenopausal and the postmenopausal women. This is probably the result of their sudden decrease in estrogen levels, and represents an equivalent of a lack of delayed transit times.

Of interest, in a mouse study looking at permeability in the intestine with induced estrogen deficiency, only the group 1 week post oophorectomy, and not the groups 4 and 8 weeks postoperatively, showed increased permeability.<sup>3</sup> It is known that loss of estrogen is associated with intestinal changes that include decreased calcium absorption leading to rapid bone loss. Again, in the human, this rapid loss reverses to slow decline after 5 years, perhaps parallel to the 8 weeks post oophorectomy in the mouse and the noted perimenopausal gastric motility changes as described in this issue of *Menopause*.<sup>1</sup> Each exemplifies recovery in the postmenopause.

Although comparison has not been made between premenopausal and postmenopausal women, it is known that estrogen has a protective effect on the mucosal barrier of the GI tract. This applies to the reinforcement of the epithelial barrier, probably by estrogen's influence on the tight junctions. It applies, as well, to the protection of the physiologic barrier, where estrogen prevents gastric acid-induced injury by promoting duodenal-induced bicarbonate secretion. This may explain why epidemiologic observations reveal that the incidence of duodenal ulcers occurs more frequently in men than women. Once again, in the absence of specific data in women, we can only hypothesize that the duodenal ulcer incidence, however, increases postmenopause.

The GI cancers in relation to menopausal status have been better explored. Here again, men have higher incidences than premenopausal women, suggesting that estrogen plays a protective role. A global assessment of over 100,000 cases of esophageal adenocarcinoma found that almost 80% occurred in men, and several studies showed that hormone therapy in postmenopausal women significantly decreased the risk of this malignancy. At least three major studies as well show a decrease in gastric cancer by as much as 50% in women on hormone therapy compared with either placebo or

Received January 23, 2019; revised and accepted January 23, 2019.

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Funding/support: None.

Financial disclosure/conflicts of interest: None reported.

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no therapy. Colorectal cancer has been studied more extensively, as it is the second most commonly diagnosed cancer in females and the third most commonly diagnosed in males. The rates of colorectal cancers are significantly higher in men than women in almost all parts of the world. The known risk factors, obesity, diet, and smoking, do not explain why men should, however, be more susceptible. This suggests a possible protective role for estrogen with regard to colon cancer. In fact, many studies indicate a reduced risk of colorectal cancer in estrogen-treated postmenopausal women. In a large meta-analysis, current estrogen therapy was highly associated with a decreased colorectal cancer risk.<sup>4</sup>

The central mechanisms that control the GI system are still being uncovered. Data available stem mostly from animal studies. It was only in 1980 that estrogen was shown to pass freely through the blood–brain barrier and affect brain–gut processing. Peptide tyrosine-tyrosine (PYY) is one of the multiple regulators of the digestion process, and its main role is to mediate the delay in the transit through the GI tract resulting in an increase in satiety. Furthermore, its satiating action is also known to originate in the central nervous system as PYY can cross the blood–brain barrier and target areas known to regulate the hypothalamus. Estrogen’s intestinal effect is to augment PYY, cholecystokinin, and glucagon-like peptide-1. All of these actions decrease appetite. Several studies have implied that estrogen may act in the prefrontal cortex to facilitate control over appetite. Although these

studies and evidence from human neuroimaging reports identify regions involved in mediating the effect of estrogens on GI factors, there are no studies directly investigating the effects on precisely defined components of neural processing of GI stimuli with and without estrogen.

Clearly, current human and animal studies support the significant role that estrogen has on multiple GI effects including protection from serious GI diseases and changing brain effects on the GI system. A pressing issue is to understand which effects of estrogen deprivation on the GI system persist and which, actually, ultimately resolve in the postmenopause. Perhaps this small pilot study of one aspect of the complex GI system in postmenopausal women will start a trend of investigation on this topic.

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