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Sex Differences in Abdominal Pain

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At a Glance

- Sex refers to a biological construct; for example, female or male.
- Gender is a socially constructed notion of what is feminine and what is masculine; for example, a person can be more feminine and less masculine, or vice versa.
- Pain is experienced differently by men and women; sex and gender both play roles.
- Women are generally more sensitive to pain than men.

Abdominal pain and functional bowel disorders

The abdomen is the area of the body between the chest and the hips. Abdominal pain is a type of visceral pain that affects internal organs such as the bowel. It can result from a number of causes ranging, for example, from something as simple as overeating, to a viral or a bacterial infection that may cause severe inflammation, or to something more serious. In the absence of a structural abnormality, abdominal pain may be an indication of a functional bowel disorder.

Functional gastrointestinal (GI) disorders are the most commonly presented GI illnesses seen by physicians in primary care or gastroenterology. In a functional bowel disorder, the primary problem is an alteration in the way the bowel works rather than an identifiable structural or biochemical cause. It generally cannot be diagnosed in a traditional way as an inflammatory, infectious, or structural abnormality that can be seen by commonly used examination, x-ray, or laboratory test. In the GI tract, functional disorders are diagnosed based on symptoms. A detailed history, physical exam, and usually limited tests help in making a diagnosis. Some situations suggest the need for more extensive testing. The symptoms of these disorders can include discomfort ranging from inconvenience to deep personal distress and pain.

His and hers

Experimental and clinical studies highlight the existence of sex-related differences in the perception of and responsiveness to painful stimuli. Sex-related differences in pain processing and responsiveness in general have been documented in experimental studies using animal models. In these studies, female responses to painful stimuli, as well as responses to pain relieving substances, depend on the stage of the reproductive cycle. Pain sensitivity was highest when the levels of circulating estrogen, a sex hormone, are at their highest just before and during ovulation, which corresponds to midway through a woman's monthly cycle.

In clinical studies, women are reportedly more likely to experience recurrent pain, have more sensitivity to pain (lower pain thresholds), and feel pain with higher intensity and less tolerance than men. Females are overrepresented in a variety of chronic pain disorders, including migraine headache, craniofacial pain, chronic low back pain, fibromyalgia, and irritable bowel syndrome (IBS). Likewise, research studies have demonstrated greater frequencies of pain-related symptoms among females than males in the general population. In this respect, a striking sex-related difference is evident in the prevalence of functional bowel disorders such as IBS, their treatment, and the perception of associated abdominal pain. Furthermore, the menstrual cycle influences gut sensitivity in female IBS patients, who often show evidence of worsening of symptoms during menses.

IBS prevalence – The female to male IBS prevalence ratios for the general population vary from 1:1 to over 2:1 across a variety of studies. Females typically are seen in larger numbers than males in medical clinics and highly specialized (tertiary) care centers. In children before puberty, functional GI disorders, such as recurrent abdominal pain and certain forms of chronic functional constipation or diarrhea, occur about equally in boys and girls. This suggests that gender-related (psychosocial) or sex-related (hormonal) changes during development may lead to the different rates of IBS apparent in adults.

IBS treatment – Sex-related differences have also emerged in the search for new IBS-specific medications.

For example, alosetron (Lotronex, a 5-HT3 antagonist) showed efficacy only in female subjects, which led the manufacturer to seek approval for the drug only as a treatment for women with IBS. Today, alosetron is approved for the treatment of IBS in women where diarrhea is the predominant bowel symptom and for whom conventional therapy for IBS has failed. It is evidence of the need for a closer look at the role of sex and gender in designing new medication for some pain conditions, at least in the case of IBS.

Menstrual cycle-related variation in IBS symptoms – Women with IBS report higher levels of IBS symptoms around their menstrual cycles, including altered motility and increased sensitivity within their gut to normal GI events. Although evidence indicates that sex hormones may influence IBS experiences, it is not clear whether worsening of GI pain is in part confused with menstrual pain or if it is entirely caused by changes in GI sensitivity. Both the lower GI tract and the female reproductive system are supplied with nerves that carry signals to the central nervous system and connect onto the same segments of the spinal cord. This leads to an overlap in the pattern of pain perceived from these organs. On the other hand, evidence suggests that the female hormones estrogen and progesterone modify GI function and slow gastric emptying of solids.

Mechanisms underlying sex-related differences in abdominal pain

Various systems could influence pain responses in a sex-related manner. These include, but are not limited to, sex hormones, internally produced (endogenous) substances that modify pain, and psychosocial factors.

Sex hormones and pain – Studies in animal models have emphasized the importance of sex hormone influence on pain responses. Sex hormones, such as the female hormones estrogen and progesterone, or the male sex hormone testosterone, can influence pain pathways in many ways by altering the processing of pain information in the peripheral (body) and central (brain and spinal cord) nervous systems. These complex actions affect the way the brain processes the body's pain sensations. Nerves to bodily organs, such as the bowel, appear to be affected by the reproductive cycle. For example, estrogen can affect how pain information is transmitted by these nerves and progesterone can influence nerve activity and how nerves respond to medications which reduce pain (local anesthetics). These effects are similar to those seen during pregnancy when estrogen and progesterone levels are very high.

Receptors are structures on cells that receive a stimulus or message and, in turn, induce a functional response in the body. In animal studies, estrogen receptors can be found in the spinal cord and in nerves within the body, including areas that process pain information from the colon and other organs in the pelvis. This information suggests that certain nerves are able to make estrogen receptors that bind estrogen and result in specific functional changes in the body. Therefore, estrogen could be involved in the increased pain sensitivity seen in females with chronic pain conditions compared to males.

A number of brain imaging studies, which visualize brain activity, have shown that uncomfortable pressure applied in the rectum using a balloon device can cause changes in the activity of specific areas of the human brain commonly associated with pain perception or sensation. (These regions include areas in the cortex and brainstem including the anterior cingulate, insula, prefrontal cortex, thalamus, and cerebellum.) In one study, despite the fact that men and women rated a pain stimulus similarly, increased activity of certain brain regions were much stronger for men.

Internal (endogenous) pain modulators – A number of experimental scientific studies have reported sex-related differences as well as hormonal effects on several internally-produced substances or pathways which modify pain within our bodies.

In studies using animal models, females and males exhibit different responses to experimental stress. Females show more pain sensitivity in response to stress compared to males. These differences appear to be effected by sex hormones such as circulating estrogen and progesterone. Additionally, pain reduction in response to pregnancy is a hormonally-influenced process unique to females.

Substance P is a protein with effects on the nervous system (a neuropeptide). Substance P is involved in the transmission of pain impulses from receptors in the body to the central nervous system. An association, in animal models, between levels of circulating estrogen and substance P concentrations has been reported in females. Observations support a role for sex hormones in the

regulation of genes, which program for different pain receptors in various parts of the body, especially the bowel. Estrogen was also found to change the role of Substance P receptors in increased bowel pain in response to stress.

NMDA is a selective agonist (stimulator) for a specific type of receptor that stimulates the cells in the nervous system. Activation of this receptor complex contributes to exciting nerve signals at sites throughout the brain and the spinal cord, and is changed by a number of internal and external substances. NMDA receptors play a key role in a wide range of physiological and disease related processes including chronic pain processing. A number of animal studies have demonstrated sex-related differences when it comes to the function of the NMDA receptors. Findings suggest that females, when exposed to the male hormone testosterone, can demonstrate the activation of NMDA-specific pain pathways seen normally in males, indicating that these pathways are affected by sex hormones.

Psychosocial factors and gender – Several factors are linked with pain sensitivity and may differ between sexes, but the extent to which this occurs remains unknown. Symptoms such as depression and anxiety are more prevalent among women than men and are associated with increased pain and other physical symptoms. Psychosocial factors, such as coping and emotional distress, which can alter pain sensitivity, contribute to sex-related differences in the experience of pain. Individuals' expectations and anxiety can alter experimental pain responses and this may occur differently in men and women. Sex roles are also associated with the quality of the pain response. A high degree of masculinity is associated with less pain sensitivity (higher pain thresholds) for men but not for women. The degree of masculinity also seems to be associated with the way the brain responds when the body is exposed to pain. Nevertheless, even after controlling for masculinity factors, the differences in pain responses between men and women remains significant.

Significance of sex differences in abdominal pain

Abdominal pain is a symptom/marker of many GI disorders, particularly IBS. Progress has been made in understanding some of the nervous system pathways, and the nervous system functional and chemical mechanisms involved in abdominal pain. However, pain in general remains an individual experience. Understanding the subjective pain experience in individuals presents unique scientific challenges. Even though the basic bodily processes may be similar, people react to pain in very different ways due to many factors, including sex and gender. These represent but one set of variables within the many interacting systems in the mind and body that can alter pain responses. The magnitude of sex-related influences on pain in relation to other factors, such as age, race, and coping skills, has yet to be determined.

Further investigation of sex differences in abdominal pain could reveal three areas of practical importance: 1) it may enhance our understanding of the functional aspects of certain pain conditions; 2) it can have implications for developing pain treatments tailored to each individual's needs; and 3) it could lead to new gender-sensitive treatments for pain, especially in the area of hormonal manipulations.

Additional Reading

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