

The tangled web of reasons for the delay in diagnosis of endometriosis in women with chronic pelvic pain: will the suffering end?

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Understanding the woman's experience with chronic pelvic pain and endometriosis is critical to decreasing her suffering. Further investigation must continue to determine the relation between endometriosis and pain, despite empirical treatment with GnRH agonists becoming routine in the United States. (*Fertil Steril*® 2006;86:1302–4. ©2006 by American Society for Reproductive Medicine.)

In this issue of *Fertility and Sterility*, Ballard and colleagues present a descriptive small study of the experiences women attending a chronic pelvic pain clinic had in reaching a diagnosis of endometriosis (1). Interestingly, they state that these women felt a sense of relief in receiving the diagnosis, suggesting that having a diagnosis, in itself, is therapeutic. Although many studies have reported a delay in the diagnosis of endometriosis, the reasons for the delay have not been known. This paper, although mainly qualitative, elucidates some reasons for this delay.

In our report of the Endometriosis Association survey of women in North America, we have similarly noted a 10-year delay from symptoms to diagnosis, with 70% reporting symptoms before age 20 and nearly 40% before age 15 (2). Others have described that women with endometriosis and pain may have a longer time to diagnosis than those with infertility (3). Those who have symptoms at a young age have a delay in diagnosis compared with those first having symptoms at an older age (3).

The delay of diagnosis in young women has been attributed to physicians not considering the diagnosis of endometriosis in adolescents, assuming that endometriosis develops over years and that insufficient time has passed from menarche. Although clinicians believe that endometriosis is uncommon in adolescent women, Laufer et al. have shown a high prevalence among those adolescents with pain unresponsive to medical therapy,

suggesting that it is a common diagnosis and should be considered in these young women (4).

Ballard et al.'s study illustrates a different point for adolescent women, that the diagnosis of endometriosis is not considered because both patient and physician may not perceive the young woman as ill. Instead, the authors describe that these young women considered themselves "unlucky" rather than "ill," which could explain a delay in seeking medical care. In addition many indicated that their pain was considered normal by family doctors. Both are reasonable explanations for not considering pain as signifying pathology in adolescent women. Pain is a subjective symptom which one person can only give an account of to another (5). Therefore, when pain begins soon after menarche, neither patient nor physician would know, for example, if dysmenorrhea was pain of a normal intensity and should be expected, or whether it was abnormal and was caused by a disease such as endometriosis.

So how does having the diagnosis of endometriosis help women? Ballard et al. suggest that it reassures them that they don't have cancer, gives them language with which to discuss their symptoms, and helps to determine strategies to manage their symptoms. These impressions should be considered in the context of what is known regarding endometriosis and pain.

Although many women may have anxiety and depression related to pain itself, women with chronic pain also have anxiety about its cause (6). Therefore, receiving a diagnosis and knowing that they are not going to die of cancer is very important. Respondents to the Endometriosis Association survey have noted that undergoing diagnostic laparoscopy was helpful (Sinaii N, unpublished data), perhaps simply because it provides a diagnosis.

Received June 16, 2006; revised and accepted June 16, 2006.
Supported by the Intramural Program of the National Institute of Child Health and Human Development and the National Institutes of Health.
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The implication of having a language to discuss symptoms suggests that endometriosis is the sole or true cause of pain. In fact, many women with endometriosis and pain also have other painful conditions. Also, the pain they have may not improve when the endometriosis lesions are treated, suggesting that the lesions may not be the cause of the pain. Ballard et al. suggest this by presenting the case of a woman who had undergone five surgical treatments with little improvement in her quality of life (1).

How to distinguish the pain from endometriosis from other causes is a dilemma we all face. In our clinical studies, we have determined other potential causes of pain that are related to endometriosis. For example, at surgery we have found that some women also have endometriosis of the appendix and may benefit from appendectomy (7). For those who do not have pain relief after excisional surgery for endometriosis, we have identified some who may have adenomyosis or endometrial glands and stroma in the myometrium (8).

Chronic pelvic pain is associated with endometriosis, but may also be associated with adhesions, pelvic inflammatory disease, bowel disease, or genitourinary conditions as well as systemic diseases. Not surprisingly, these conditions often co-exist. We have reported that members of the Endometriosis Association have chronic pain and fatigue states of fibromyalgia and chronic fatigue syndrome at a higher prevalence than women in the general population (2).

In a survey of 136 general practices in the United Kingdom who had a contact with nearly 300,000 women, Zondervan et al. found that women with chronic pelvic pain whose final diagnosis was endometriosis often have the highest referral rates and have the greatest number of diagnoses (9). They also determined that half of nearly 4,000 women with chronic pelvic pain responding to a postal questionnaire had genitourinary symptoms, irritable bowel syndrome, or both (10). Furthermore, over 80% of women with chronic pelvic pain reported dysmenorrhea compared with about 60% of those without. The severity of dysmenorrhea was significantly greater among those with additional genitourinary symptoms or irritable bowel syndrome than those with chronic pelvic pain only.

The interrelationship among pain, endometriosis and other conditions is complex. Berkley, through her research in rats, has provided some insights regarding cross-system effects between the reproductive organs, bladder, and colon, suggesting that the pathophysiology in one organ can influence the physiology (or pathophysiology) in others (11). For example, a surgical model of endometriosis in rats produces vaginal hyperalgesia. In addition, these animals also experience an increase in pain behaviors induced by a ureteral stone.

Similar effects of peripheral sensitization are likely to occur in women, because pain associated with endometriosis is one type of regional pain syndrome. Furthermore, women with endometriosis and pain have been shown to experience

a lower pain threshold in their hands, which are parts of the body in which they are not having pain; this process is called central sensitization (12).

Given that many women with endometriosis also have other conditions, how does having the particular diagnosis of endometriosis actually help them discuss their symptoms? Is it only because it legitimizes their symptoms and allows them to have social supports? How are these other diagnoses (and treatments for these other conditions) considered?

Ballard et al. assert that intermittent use of hormonal treatments suppresses symptoms and delayed the diagnosis. This is puzzling, because these very hormonal treatments of oral contraceptives and pregnancy, in fact, may be the same management strategies patients turn to once they have the diagnosis. The interrelationship among pain, endometriosis, and hormonal therapy is complex.

The ectopic endometrial tissue may be innervated and sensitive to estrogen (13). However, it is not known how the use of oral contraceptives masks the diagnosis. Do oral contraceptives actually prevent the development of endometriosis in young women? Do they suppress the painful experience of endometriosis by decreasing menstrual flow or suppressing lesions themselves? Or do oral contraceptives influence the experience of pain itself? It would be helpful to determine whether women who used these treatments previously (who may have had a decrease in pain which then theoretically masked the diagnosis of endometriosis) later find these hormonal treatments effective once they have the diagnosis.

One of the most important messages of this study is that inappropriate diagnostic tests are used, which would seem to refer only to ultrasound. Ultrasound can be helpful in identifying endometriomas, but it is not helpful in identifying peritoneal disease or adhesions (14). Thus, although ultrasound can be used to determine whether there is an ovarian mass or tumor, routine ultrasound does not usually aid in the diagnosis of chronic pelvic pain and, in fact, may discount the woman's pain and suffering.

So what is an appropriate diagnostic test for endometriosis? Unfortunately, other than the use of ultrasound for endometriomas, we don't yet have any reliable, noninvasive tests. The gold standard has been laparoscopic diagnosis by visual inspection. Histologic confirmation of at least one lesion is probably ideal and may be useful, especially in those with minimal and mild disease (15). Negative histology, however, does not exclude the diagnosis.

Having the diagnosis of endometriosis, however, does not illustrate how that diagnosis is related to chronic pelvic pain. A recent review by Fauconnier and Chapron tries to clarify how chronic pain symptoms relate to the characteristics of lesions (16). They conclude that endometriosis may be responsible for chronic pelvic pain symptoms in more than half of the confirmed cases, based on randomized trials using a placebo arm. In considering deeply infiltrating endometri-

osis, in particular, they cite histologic and pathophysiologic evidence that associated pain symptoms are likely related to compression or infiltration of nerves by the lesions. Importantly, they illustrate that the painful symptoms caused by deeply infiltrating lesions have characteristics unique to the anatomic location involved; thus, type of endometriosis implants is related to pain location. This suggests that a careful analysis of chronic pelvic pain symptom characteristics is useful in the diagnosis and therapeutic management of endometriosis-related pain in those with deep infiltrating lesions.

Fauconnier and Chapron's summary and many studies in the last decade have improved the understanding of the relation between pain and endometriosis. Surveys of Endometriosis Association members and women with chronic pelvic pain, reviews of general practice patterns in the management of pelvic pain, rat and other animal models, and clinical studies elucidating potential treatments have all enhanced our knowledge. Yet, we still have not developed a standard language and system of assessing, discussing and treating chronic pelvic pain in women with endometriosis, despite clinicians developing classification systems and patients composing questionnaires for patients (5).

Perhaps this is because chronic pelvic pain is a generic type of regional pain syndrome and endometriosis is one example. Regardless of the reasons, more basic, translational, and clinical research is necessary to determine the relation between endometriosis and pain.

Recently, the American College of Obstetricians and Gynecologists Committee on Adolescent Care wrote a Committee Opinion regarding endometriosis in adolescents which has changed the diagnosis and treatment of endometriosis in the United States (17). They recommend that laparoscopic evaluation be offered to adolescents under the age of 18 years if they have persistent pain while taking oral contraceptives and non-steroidal antiinflammatory agents. However, if she is older than 18 years and has a negative assessment for an ovarian mass or tumor, she can be offered empirical therapy with a GnRH agonist. If the pain subsides with the use of GnRH agonist, it is presumed that the woman has endometriosis. This empirical treatment is not offered to adolescents under 18 years old, because the effects of these medications on bone formation and long-term bone density is unknown.

These guidelines have resulted in a change in the treatment of women with pelvic pain in the United States. Women no longer must undergo laparoscopic evaluation to be given the diagnosis of endometriosis. The response to GnRH agonists is considered sufficient to make the diagnosis. In considering the study on which this recommendation was based, about 80% of women taking either leuprolide or placebo had endometriosis. Interestingly, those who did not have endometriosis on laparoscopy also had an improvement in pain.

What will the impact of the use of empirical therapy be on the diagnosis of endometriosis or the evaluation of chronic

pelvic pain? How will empirical therapy relate to the physician's clinical assessment of chronic pelvic pain in these women? Will the physicians taking care of women with chronic pain use this empirical treatment freely to make the diagnosis or only after systematically evaluating the patient? Will the women who respond to empirical treatment (along with their doctors) believe that they have endometriosis? Will those who do not respond believe they do not have endometriosis? Will women with chronic pelvic pain suffer less? Only time will tell.

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