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Mysteries of endometriosis pain: Chien-Tien Hsu Memorial Lecture 2009

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Abstract

The more that one looks at the condition endometriosis, the more one realises that it is a unique and complex condition exhibiting a bizarre range of deviations from normal endometrial and myometrial physiology, and presenting with a challenging range of pain-related symptoms. The changing nature of the pain is not well defined, and the molecular mechanisms leading to pain generation are far from clear. Recent research has begun to reveal some of these links between expression of unusual molecules in the eutopic endometrium and ectopic lesions, microanatomical changes in the pelvic nervous sytem, neuronal dysfunction and the later development of neuropathic pain. A better understanding of these mechanisms will undoubtedly lead to improved use of current medical and surgical treatments, and to the development of novel treatments in the future.

Key words: endometriosis, endometrium, nerve fibers, pelvic pain.

Introduction

This most prestigious lecture in Asian obstetrics and gynecology is given once every two years in honor of Professor Chien-Tien Hsu, one of the true legends of obstetrics and gynecology on this continent and one of the founders of the Asia and Oceania Federation of Obstetrics and Gynecology (AOFOG). Professor Hsu's clinical interests were primarily in oncology and reproductive endocrinology, and my illustrious predecessors as Chien-Tien Hsu Memorial lecturers have spoken exclusively on these themes.

Although I may appear to be departing from these themes in talking about the non-malignant condition of endometriosis, and indeed not even about its impact on fertility and endocrinology, this bizarre and variable condition exhibits many features which point towards a pseudo-malignant disease.[1] Endometriosis exhibits loss of control of cellular proliferation, local infiltration and spread into adjacent deep tissues, disturbed angiogenesis, expression of proto-oncogenes, disturbed apoptosis, occasional distant spread and a tendency to recur after treatment – all being important features of malignancy. Nevertheless, these processes do not aggressively continue and inexorably progress, as in most true malignancies. Additionally, endometriosis is actually associated with a long-term risk of true ovarian malignancy, especially following recurrent ovarian endometriomas (with a relative risk of around 2.0).[1]

Yet, in many ways, the behavior of endometriosis is very different in the majority of sufferers. The keynote of the condition is variability (Table 1) and in most women the condition is unquestionably 'benign'. It is only in a minority that the condition exhibits the features listed in the previous paragraph to the extent that the analogy with malignancy really holds. In many of these severely affected women, the intensity and persistence of pain is as difficult to deal with as in any case of bony metastases from cancer. Pain will be the central theme of this lecture.

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Table 1 Endometriosis is a highly variable condition

High levels of variability in:
Age of onset of symptoms
Constellation of presenting symptoms
Types and severity of pain
Site and extent of pathology
Coexistence of other pathologies
Response to treatment
Rate of recurrence of symptoms and disease

Pain is the Central Challenge

Pelvic pain is universally recognized as the key symptom in endometriosis; the primary reason why the patient consults her doctor. Infertility is also a common symptom of endometriosis, but most of these patients will additionally complain of pain. Endometriotic pelvic pain may be well recognized, but many doctors, including gynecologists, think only in terms of the common triad of dysmenorrhoea, deep dyspareunia and pain with a bowel motion. Yet, there is now ample information to demonstrate that many women experience a much more complex range of pains, which are addressed in the next section. This lack of awareness of the variations in endometriotic pain may well be responsible for the distressing delays in diagnosis, which average 8–10 years from the onset of symptoms.[2] These delays are even greater in those with onset of symptoms in early adolescence, a time of life during which many doctors still believe that endometriosis does not occur. A further factor contributing to a delay in diagnosis is the failure of patients to inform their doctor of pain symptoms. The decision to complain of pain to doctors, or failure to complain, are very personal decisions by individual patients, but it is clear that in most, if not all countries many women believe that their 'endometriotic pains' are a natural aspect of women's reproductive life, and hence they do not inform their doctor.

To be fair, for doctors attempting to manage endometriosis, it is one of the most variable of all gynecological conditions with consequent diagnosis challenges (Table 1). No other benign condition of the reproductive tract causes such troublesome or variable pain. Endometriosis is generally defined as the occurrence of tissue histologically similar to endometrium, but implanted outside the uterus. It is most usually found on the pelvic peritoneum, on the surface of the ovaries, bowel or bladder, on or in the utero-sacral ligaments, ovaries, recto-vaginal septum and rarely in other sites such as diaphragm, umbilicus, pleura, lungs, abdominal scars or elsewhere.

No other benign condition of the reproductive tract exhibits such a bizarre range of deviations from normal physiology of the endometrium. Indeed, there is increasing evidence to suggest that endometriosis is a disease originating from abnormalities of endometrial function.[3,4] There is now highly convincing evidence of disturbances of multiple molecular systems involving structural, metabolic and immune systems.[4–7] These include cytokeratins, integrins, vimentin, heat-shock proteins, smooth muscle actin, adhesion molecules, transcription factors, apoptosis proteins, aromatase enzyme expression, oxidative pathways and a wide range of angiogenic, lymph-angiogenic and neurogenic systems.

Symptoms of Pain in Endometriosis Sufferers

The classical symptoms of endometriosis, which should be recognized by all doctors, include secondary (congestive) dysmenorrhoea, deep dyspareunia, bowel motion pain, heavy menstrual bleeding and infertility. However, examination of the literature and focus groups indicate that menstrual cycle and menstruation-related pains are much more extensive and complex than this (Table 2). Indeed, the pains of endometriosis are only part of a unique but highly variable symptom complex (Table 3).

The characteristics of menstrual pain (dysmenorrhoea) are described by most women as intense, unbearable, miserable, cramping, gnawing, crushing or pressing.[8] The dominant sites of pain are central and low abdomen (92% of women with dysmenorrhoea), deep pelvic area (41%), lower back (50%) and variously referred into thighs, loin, groin, rectal area and umbilicus.[8] The severity of the pain was much greater than in a group of 'control' women,[8] but interestingly the day of maximum severity of pain was day 1–2 in both endometriosis sufferers and the group of women with no specific gynecological complaint.

Painful gastrointestinal symptoms are often overlooked, but colicky pains and irritable bowel-type symptoms are experienced by 82% of women with endometriosis.[8] It is said that the key difference between so-called irritable bowel syndrome and typical endometriosis-related bowel symptoms is that in irritable bowel syndrome the colic is relieved by a bowel motion, whereas in endometriosis it is not.

Table 2 Different types of pain associated with endometriosis[8]

1. Types of menstrual cycle pain
   Premenstrual: general pelvic, back
   Peri-menstrual: uterine and general, back
   Mid-cycle: uterine and ovarian
   Back, leg and loin pain: referred
   Bowel pain: from closely located lesions
   Peri- and post-micturition pain: from closely located peritoneal lesions, or from bladder
   From other sites
2. Peri-menstrual pain (Dysmenorrhoea):
   Dominant pain described as:
   – intense, unbearable, miserable (89%)
   – cramping, gnawing, crushing, pressing (88%)
   Dominant sites of pain:
   – central/low abdomen (92%)
   – deep pelvic area (41%)
   – lower back (50%)
   – thighs, loins, rectal area, umbilicus
   Much more severe than in women with no gynaecological disease
   Worst on days 1–2 of menses, begins premenstrually when less severe
3. Nerve entrapment
   Pain due to anatomical nerve distortion by scarred, but often active, endometriotic lesions
   Recognised nerve entrapment:
   – referred pain along the path of the trapped nerve, sometimes with associated functional disturbance (especially muscle)
   – sciatic and obturator nerves
   Postulated nerve entrapment:
   – deep infiltrating lesions, especially in recto-vaginal septum (distortion of small nerve trunks in dense enteric and endometriotic nerve plexuses within highly fibrotic endometriosis lesions)
4. Neuropathic pains
   – increasingly recognised as being a significant component of persistent endometriosis pain
   – arises from damage to nerves (peripheral or central)
   – may be exacerbated by repeated surgery
   – therapies are often only partially successful
   – Gabapentin; pregabalin (GABA analogues)
5. Other pains:
   – hyperalgesia; allodynia
   – Myofascial dysfunction (trigger points)
   – lowered pain pressure threshold
   – these are evidence of central nervous system sensitisation

Table 3 Clinical endometriosis: a highly variable symptom complex[8] (endometriosis cases: $n = 529$; controls: $n = 208$)

Pain (92%); no pain (6–8%)
Extreme lethargy (97%)
Gastrointestinal symptoms (96%)
Urinary tract symptoms (44%)
Low resistance to infection (43%)
Low grade fever (42%)
Increased predisposition to autoimmune conditions
Genital tract bleeding:
– heavy menstrual bleeding (65%); premenstrual spotting (63%)

Painful abdominal bloating is another overlooked endometriosis symptom, but one which can be terribly distressing in some women. Around 71% of women with endometriosis will experience painful bloating every cycle, while another 25% will sometimes experience it. Many of these women will possess two different wardrobes to accommodate the cyclical changes in abdominal girth, changes which can be objectively measured.[9] Intermittent diarrhea (78%) and constipation (76%) are very frequent in the peri-menstrual stage, and pain with a bowel motion is also very common (67%) and exacerbated in the peri-menstrual stage. Bleeding from the bowel during menstruation is also more common than generally recognized (around 20%).

Nerve entrapment pain is a relatively rare type of endometriosis pain due to anatomical nerve distortion by active, fibrotic lesions, especially around the sciatic and obturator nerves.[10,11] This pain is usually referred along the path of the trapped nerve, sometimes with associated functional disturbance, especially of muscle power. Postulated nerve entrapment occurs in the complex fibrous and hypertrophic deep invasive endometriotic lesions in the recto-vaginal septum, where distortion of nerve trunks appears to be occurring.[12]

Neuropathic and Other Types of Pain

Neuropathic pain is being increasingly recognized as a significant component of persistent endometriosis pain.[13] Neuropathic pain arises from damage to peripheral or central nerve fibers, resulting in erratic or persistent axonal discharges. These persistent stimuli can set up abnormal neural circuits at a spinal cord or central level resulting in persistent, prolonged or intermittent signals to the central processing and perception centres. This may lead to persistent perception of pain, long after the original stimulus may have been removed.

A number of questionnaires have been designed to identify the neuropathic components of pain.[14,15] One

study suggests that neuropathic pain is uncommon in women with chronic pelvic pain,[15] but there has been no comprehensive study on women with the persistent and debilitating types of endometriotic pain.

One concern about the consequences of pelvic surgery for endometriosis, especially repeated surgery, is that damage to nerve fibers, especially repeated damage, may trigger persistent, abnormal discharges from these plentiful, damaged and regenerating pelvic and endometriotic nerve fibers, leading to the development of neuropathic pain.

Other types of pain are also being reported in many women with endometriosis. These mainly involve altered perception of pain. Hyperalgesia involves the perception of pain as being more severe than expected from the stimulus, for example, a lowered pain threshold.[16] Allodynia is the perception of pain from a stimulus that does not usually produce pain. In myofascial dysfunction there may be trigger points which produce a painful response when stimulated. All of these types of altered pain perception are evidence of sensitization at a central nervous system level.[16]

The Discovery of Endometrial Nerve Fibers

Several investigators have reported nerve fibers in ectopic endometriotic lesions[12,17] and have described the presence of certain types of nerve fibers in some of the lesions. It was suggested that these may have a role in the mediation of pain. We decided to establish a series of investigations to comprehensively explore the innervation of the uterus and ectopic lesions in women with a range of endometriosis symptoms. We decided, in the first instance, to utilize a robust pan-neuronal marker, protein gene product 9.5 (PGP9.5), which was becoming the neurophysiologist's preferred immunohistochemical marker for defining the presence of all nerve fibers in tissue sections. This antibody has minimal cross-reaction with other tissue types.[18]

This was followed up with a comprehensive investigation of a range of different immuno-histochemical markers recognizing autonomic, sensory and myelinated nerve fibers. Neurofilament was used to define myelinated nerve fibers, which were apparently sensory A-delta fibers. Substance P (SP) and calcitonin gene-related peptide (CGRP) were used to identify unmyelinated sensory C nerve fibers. Neuropeptide Y was used to identify adrenergic (sympathetic) nerve fibers and vasointestinal peptide identified cholinergic (parasympathetic) fibers. Growth associated protein-43 is expressed on growing nerve fibers. The situation is somewhat more complex than described above, and the accurate identification of nerve fiber types is quite difficult (Table 4).

Table 4 Identification of nerve fibre types in endometrium and endometriotic lesions

Fine nerve fibres in endometrium (functional layer)
Immuno-histochemical localisation with specific tissue markers for nerve fibres (antibodies for several molecules expressed by nerve fibres)
Pan-neuronal marker (protein gene product 9.5): specifically stains all nerve fibers
Stains for myelinated nerve fibers (neurofilament, stains A delta fibers)
Neurotransmitters and other markers for nerve fibers of different functions
Most of these nerve fibers are, in fact, unmyelinated C fibers
Sensory and autonomic C nerve fibers
These fine unmyelinated nerve fibers in the functional layer of eutopic endometrium expressed:
– vasointestinal peptide (cholinergic)
– neuropeptide Y (adrenergic)
– substance P (sensory)
– calcitonin gene-related peptide (sensory)

The first striking observation was that fine, unmyelinated nerve fibers are present in surprisingly high densities in both the functional and basal layers of endometrium of women with endometriosis, while virtually none are found in the endometrium of women with no endometriosis (Fig. 1).[18] It became apparent that the functional layer of normal endometrium is one of the few – or perhaps the only – tissue in the body which is not normally innervated. Previous studies using less precise technologies have failed to agree on this conclusion.[19,20] With careful scrutiny, small numbers of fine unmyelinated nerve fibers can be identified with PGP9.5 in the basal endometrium of some women without endometriosis, but rarely in the functional layer.[18] In women with endometriosis, substantial nerve trunks can often be identified at the endometrial-myometrial interface. These are never seen in the absence of endometriosis.

Studies with multiple markers for different types of nerve fibers revealed that the unmyelinated nerve fibers in the endometrial functional layer were a mixture of sensory C, sympathetic and parasympathetic fibers.[21] Myelinated sensory A-delta nerve fibers were occasionally seen in basal endometrium but never in the functional layer. In women with no endometriosis, myelinated nerve fibers were only found in

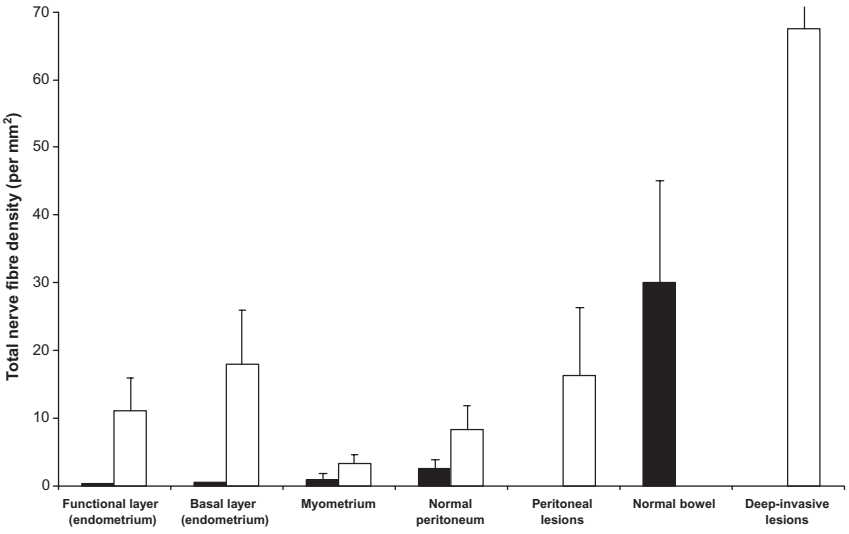

Figure 1 Mean (±standard deviation) nerve fiber densities (protein gene product 9.5; per mm^2) in the uterus, peritoneum and ectopic lesions in women with and without endometriosis.

myometrium.[18] These nerve fibers are not homogeneously distributed through the endometrium but appear in clusters. Nerve fibers can be identified within a few microns of the luminal, epithelial layer of the endometrium.

The density of nerve fibers in myometrium is much lower than in endometrium, but women with endometriosis have much more densely innervated myometrium than women without endometriosis.[18]

Presumably, the high densities of nerve fibers present in endometrium and myometrium in women with endometriosis arise from the pre-existing innervation of the myometrium through a process of branching and proliferation. This explanation is supported by the observation of substantial nerve trunks at the endometrial-myometrial interface and the clustering of fine nerve fibers through the endometrium.

Nerve Fibers in Endometriotic Lesions

As others have described, nerve fibers can be identified within peritoneal,[17] ovarian endometrioma[22] and deep infiltrating endometriotic[12] lesions. We have comprehensively analyzed and defined the innervation of these lesions[23,24] and found densities in peritoneal lesions comparable to the eutopic endometrium (Fig. 1).[23] These nerve fibers in lesions expressed all the markers we studied and included sensory C, sympathetic, parasympathetic and myelinated sensory A-delta fibers. Sometimes sizeable nerve trunks were identified passing though peritoneal lesions, something never seen in normal peritoneum.[23]

Somewhat surprising was the finding of a much greater density of nerve fibers in deep, infiltrating lesions (Fig. 1). The density in lesions of the uterosacral ligaments was more than double that found in peritoneal lesions, while densities in lesions infiltrating the rectal wall were even higher still.[24] In several intestinal lesions densities of over 300 nerve fibers per mm^2 were observed, compared with densities around 15 per mm^2 in peritoneal lesions.[23,24] It seems probable that the invading endometriosis bringing its own nerve supply links up with the intrinsic (enteric) nerve plexus of the bowel, resulting in excessive branching and proliferation of multiple nerve fibers. The density of the normal enteric plexus of the bowel is around 30 fibers/mm^2.

These nerve fibers presumably arise from the normal local innervation of the peritoneum, endometrium or bowel through a branching and proliferation process.

Nerve Growth Factor and its Receptors

Why do these nerve fibers appear in eutopic endometrium and ectopic lesions? There must be some stimulus to local nerve growth, and nerve growth factor (NGF) seemed an obvious candidate. In fact, NGF is intensely expressed in the glands and stroma of the functional and basal layers of endometrium in women with endometriosis, whereas it is barely expressed at all (a trace in the basal layer) in women with no endometriosis.[18] NGF is also intensely expressed in ectopic lesions.[23] Other neurotrophins may also play a role.

NGF interacts with two specific receptors: TRK-A (a high affinity receptor) and p75 (a low affinity receptor). These receptors are barely detectable in normal endometrium, but are both intensely expressed in nerve fibers and stroma in eutopic endometrium.[18] Similarly, they are intensely expressed in the stroma of ectopic lesions. It seems logical that this combination of up-regulated neurotrophin and its receptors would be a potent stimulus to branching and ingrowth of new nerve fibers.

Mechanisms of Pain Generation

This is the area of greatest mystery within the topic of endometriosis pain. It has generally been tacitly assumed that nerve fibers already present in the pelvis somehow become stimulated by the ectopic lesions, presumably by some substance which is released from the lesions at particular times during the menstrual cycle. Leading candidates for such specific substances include the prostaglandins, bradykinin and histamine, but little work has been carried out in this area in studying pelvic pain in women.

Pain signals in sensory nerve fibers are generated through receptors called nociceptors.[25] They are responsive to 'noxious' stimuli which have the potential to do harm, and have the potential to trigger a reflex response. They send signals which initiate the sensation of pain. The fast signals travel in the myelinated, sensory A-delta fibers, and the slower, more persistent signals travel in the unmyelinated, sensory C nerve fibers. These signals are processed in the dorsal root ganglia and the lower spinal cord, before onward transmission of a modified signal to the thalamus, limbic system and higher centers, where pain is perceived and the emotional response is developed.

In visceral organs, nociceptors tend to respond to excessive pressure, excessive stretch, 'inflammatory' processes and a range of injurious chemical substances. The nociceptors in endometriotic lesions and eutopic endometrium have not been specifically studied, but it is known that pelvic nociceptors in adjacent organs are stimulated strongly by nerve growth factor and prostaglandin E_2.[26,27] They are also significantly sensitized by oestrogen. Bradykinin, histamine and interleukin-1 are probably also important sensitizers. In fact, the nociceptor is an incredibly complex organelle which can be stimulated, sensitized, inhibited or otherwise regulated by hundreds of extrinsic and intrinsic molecules, many of these arising in immune competent cells, such as mast cells, macrophages, dendritic cells, neutrophils, natural killer cells, plasma cells and probably others. The complexity may even rival the synapse, which is the most complex organelle in the body, with over 1500 synapse-associated proteins having been identified to date.

There is little doubt that immune cells will be shown to play important roles in pain generation in endometriosis, both in ectopic lesions and in the uterus. Macrophage numbers and function are greatly modified in ectopic lesions, peritoneal fluid and eutopic endometrium of women with endometriosis.[28,29] In ectopic lesions, there is a direct relationship between the numbers of macrophages and the density of nerve fibers.[30] There is also a substantial disturbance in the numbers of immature and mature dendritic cells in eutopic endometrium and in the ectopic lesions in women with endometriosis.[31,32] Mast cells may have an interesting microanatomical and functional relationship with nerve fibers at the endometrial-myometrial interface where, in endometriosis, activated mast cells are abundant on the myometrial side, but in very low density in the endometrium.[33]

Another specialized feature of the eutopic endometrium in endometriosis, which may or may not relate to mechanisms of pain, is the significantly increased numbers of neuro-endocrine cells present in endometrial glands, compared to women without the disease.[34] These neuro-endocrine cells have varied functions in different organs, but they have not been previously studied in the human uterus, let alone in endometriosis.

Implications of Abundant Nerve Fiber Presence

Many questions arise as to the new directions which will be required to understand the roles and functions of these eutopic and ectopic nerve fibers. How do the presence and function of the different types of nerve fibers react to the types and presence of symptoms? What is the role of nerve fibers in the pathogenesis of endometriosis? What happens to them during treatment? What is the potential for development and delivery of long-acting nociceptor blockers? What is the potential for development and delivery of NGF blockers? What is the potential for developing a less invasive means, than laparoscopy, for the diagnosis of endometriosis?

There is also the fascination of what may be happening to these nerve fibers during menstruation. Some

nerve fibers lie very close to the epithelial surface of the endometrium, so are these fibers damaged and partially 'shed' during menstruation, then re-modeled and re-grew during the subsequent proliferative phase? Do these nerve fibers remain intact? Is there significant re-growth of these multiple nerve fibers every menstrual cycle? What do we know of plasticity of myometrial nerve plexus fibers during the normal menstrual cycle, and how does this change during endometriosis? Are the nociceptors in endometrium sensitized by the process of menstrual breakdown? Are there other examples in the body of regular, rapid re-modeling of nerve fibers under any similar circumstances? How does this damage to nerve fibers relate to symptoms? How does this damage and breakdown of nerve fibers relate to the pathophysiology of development of endometriosis? Do these nerve fibers in endometrium precede development of endometriosis lesions in the peritoneal cavity?

Table 5 Endometrial nerve fiber detection and identification in women presenting with pelvic pain or infertility

Identification of individual nerve fiber types is difficult
These endometrial nerve fibers are probably a combination of sensory C and autonomic C fibers
Sympathetic fibers strongly express neuropeptide Y, noradrenaline (adrenergic) and adenosine tri-phosphate; but sometimes also vasointestinal peptide and acetyl choline [ACh, sympathetic fibers are controlled by cell bodies in the thoracic and lumbar regions]
Parasympathetic fibers strongly express vasointestinal peptide (and co-express nitric oxide synthase) and ACh (cholinergic), but sometimes also neuropeptide Y [parasympathetic fibers are controlled by cell bodies in the cranial and sacral regions]
Sensory fibers express substance P and calcitorin gene-related peptide (but sometimes may also express neurofilament, vasointestinal peptide and neuropeptide Y)

Potential for the Diagnosis of Endometriosis by an Endometrial Biopsy

It seemed to us that the presence of nerve fibers in endometrium was so predictable that it could be explored as the basis of a diagnostic test. In a pilot trial of endometrial biopsies collected from 20 women with proven endometriosis and 18 women with no endometriosis (for the detection of endometrial nerve fibers using PGP9.5) all of the women with endometriosis had detectable nerve fibers while none of the women without endometriosis had detectable nerve fibers.[35] The sensitivity and specificity of 100% seemed to be too good to be true, and we immediately set up a double-blind trial with the aim of recruiting around 100 women.[36]

We recruited 99 women who presented with pelvic pain and/or infertility and were scheduled for diagnostic laparoscopy. The assessment of endometriosis at laparoscopy, carried out by one of five experienced gynecological endoscopists, was maintained in a separate database held separately from the laboratory assessment of endometrial nerve fibers. The databases were only brought together by a third person at the completion of the trial. Endometrial nerve fibers were detected in 63 of 64 women in whom endometriosis was surgically diagnosed (Table 5). A 43-year-old women with no endometrial nerve fibers visualized in the biopsy had clear evidence of stage IV endometriosis at laparoscopy.[36]

Endometrial nerve fibers were not detected in 29 out of 35 women in whom endometriosis was excluded at laparoscopy. However, six women with no detected endometriosis had nerve fibers present in the endometrial biopsy. Four of these women had classic pelvic pain and infertility, while one had a single spot of adhesions in the Pouch of Douglas (not convincing of endometriosis) and one case had had endometriosis diagnosed 7 years previously, but no current visible lesions.[36]

These two studies offer promise that an endometrial biopsy can be used as a much less invasive and less expensive test for endometriosis than diagnostic laparoscopy carried out by an expert, and with equivalent reliability. Neither technique can be expected to provide 100% reliability for detection or exclusion, but both must be close. Endometrial biopsy can be carried out in an outpatient clinic, usually without local analgesia and offers the potential for much earlier diagnosis and more careful planning of future medical, surgical or infertility therapy. Even though this type of approach is an advance over laparoscopy, a reasonably reliable serum test would have even greater utility.

Effects of Hormonal Therapy on Nerve Fibers

In women with endometriosis who were being actively treated with oral progestogens or combined oral

contraceptives, nerve fibers were no longer detectable in the majority.[37] In three treated women out of 26, small numbers of nerve fibers were detected in the functional layer, but these only expressed vasointestinal peptide and neuropeptide Y (and hence were autonomic fibers) while none expressed the sensory nerve fiber markers SP and CGRP. This finding was accompanied by an almost complete loss of expression of NGF and its receptors. These combined findings implied that there should have been an almost complete inhibition of pain signals originating within the uterus itself.

By contrast, in women on hormonal treatment who were still experiencing sufficient symptoms to require a repeat laparoscopy all (18 out of 18) had nerve fibers still detectable in biopsies of their peritoneal lesions, albeit at a much reduced density.[38] These nerve fibers still expressed weak staining for SP and CGRP suggesting that some sensory fibers were still present.

There are still many unanswered questions concerning the presence and function of nerve fibers during and after medical and surgical therapies and their relationship to persisting pain. It should also be appreciated that surgical excision is not always effective.[39] There is a need to explore, much more actively, the place of progesterone receptor modulators[40] and aromatase inhibitors,[41] alone and in combination, and also the place of the long-acting progestogen delivery systems alone and in combination[42–44]

Conclusions

Women with endometriosis and pelvic pain almost always have fine, unmyelinated nerve fibers present in the functional layer of endometrium, and these nerve fibers are also greatly increased in the myometrium. Women without endometriosis almost never have these nerve fibers. These nerve fibers may also play a role in pain generation. The presence of these nerve fibers may allow reliable diagnosis of endometriosis without recourse to laparoscopy. The presence of these nerve fibers may predate the development of endometriotic lesions and symptoms. There may be important implications of nerve fiber presence for understanding of the impact of treatments and for evolving new treatments.

Endometriosis causes more recurrent distress through pelvic pain than any other gynecological condition in Western society. The mechanisms of development, triggering and persistence of this pain are very poorly understood, but some women with endometriosis have no pain – and this also is very poorly understood. The condition is highly variable and the diagnosis is often missed. Management is often unsatisfactory.

I believe that we, as gynecologists, have failed our patients. We have failed to understand the different types of pain. We have failed to understand the complexities or the factors which influence these pains. We have focused solely on lesions, we cut, burn and hope, and then repeat the surgery – later! We spend hours operating, but little time talking with the patient about their individual needs. We know that teaching pain-coping skills is critical, but is very difficult, and we as a profession put limited effort into the development of effective means of teaching pain-coping skills to women with chronic pelvic pain. We need to recognize the need for individualization of management.

Only when we recognize that this complex disease, endometriosis, is a systemic disease, with implications far beyond the reproductive tract and the recognizable lesions, will we be able to manage this disease most effectively.

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