9-1-2021

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It is widely accepted that endometriosis is associated with multiple chronic inflammatory conditions and localized pain. Women with endometriosis can have cyclic or noncyclic pelvic pain, progressive dysmenorrhea, dysuria, deep dyspareunia, and painful endometriosis lesions in the abdominal wall and the diaphragm, or they may be asymptomatic.

Endometriosis-associated pain has been explained by the inflammatory reaction around endometriosis lesions, nerve infiltration including large somatic nerves, or distention of lesions with trapped blood. Unfortunately, much less attention has been paid to the variability of pain caused by individual lesions. This variability means that, clinically, pain severity correlates poorly with the severity or location of endometriosis lesions. Not all endometriosis lesions are painful, and clinically about 50% of women with typical lesions, 10% of women with cystic ovarian lesions, and 5% of women with deep endometriosis do not have pain. This variability has been confirmed by clinical examination of rectovaginal deep endometriosis lesions, with pain varying from no pain to severe pain. Furthermore, by conscious pain mapping, the pain of typical and subtle lesions varies from no pain in half of lesions to severe pain.[1] In addition, painful lesions are associated with a painful peritoneum around the lesions,[2] and the severity and area of this painful peritoneum is also highly variable. Individual endometriosis lesions can be associated with peritoneal pain up to a distance of 27 mm from typical or subtle lesions.[1] Variability of pain around small, clinically unrecognized, eventually retroperitoneal lesions is not known.

The pathophysiology of this variability in pain associated with individual lesions and of pain at a distance of up to 27 mm is not yet understood. Pain variability could be explained by differences in inflammation; by small, unrecognized retroperitoneal lesions; or by surrounding nerve density.

These differences might be a consequence of genetic–epigenetic differences in the lesions, as suggested in genetic–epigenetic theory[3] and as supported by the clonality of endometriosis lesions and the biochemical variability of lesions (e.g., variability in aromatase activity or progesterone resistance in up to one-third of symptomatic women). The exact mechanism of this variability is unknown. One can only speculate which sets of genes might be activated or repressed, and why. The underlying molecular biological pathways are unknown.

Differences could also be a consequence of a different immunological and inflammatory reaction. However, we do not understand which substances cause activation of peritoneal nociceptors or neuroinflammation in and around the lesions or at a distance from the lesions. Pain or neuroinflammation caused by endometriosis at a distance without direct contact may be clinically important. Anatomically, the sympathetic and parasympathetic nerves,

J Obstet Gynaecol Can 2021;43(9):1035–1036

https://doi.org/10.1016/j.jogc.2021.06.002

the inferior hypogastric plexus, and most somatic nerves (e.g., the obturator, pudendal, femoral, and sciatic nerves) are well within 27 mm from potential endometriosis lesions. The bottom of peritoneal pockets will be much closer to these nerve structures. Neuroinflammation at a distance might explain cyclic sciatic pain that resolves in a large majority of women after excision of peritoneal pockets.[4] Neuroinflammation by missed endometriosis lesions might suggest that peritoneal pockets are a cause of pelvic pain, in addition to endometriosis.[5] An alternative hypothesis is that endometriosis-associated pain may be referred pain originating from sympathetic/parasympathetic pelvic nerves to somatic nerves as they travel close to each other along the spinal cord, rather than the result of direct irritation of the lumbosacral plexus.[4]

Neuroinflammation at a distance from endometriosis also explains a series of clinical observations. We were recently surprised that, in three women, cyclic symptoms of neuroinflammation of the obturator nerve disappeared after removal of peritoneal pockets with endometriosis lesions. We were also surprised to find that, in all three women, the obturator nerve was located immediately underneath the peritoneum of the pocket (submitted for publication).

After excision of over 2000 deep endometriosis nodules between 1990 and 2005, I (the first author of this editorial) never explored the sciatic or the pudendal nerve. Yet my clinical impression was that, in many women with cyclic sciatic pain or pain suggestive of Alcock syndrome (pudendal nerve entrapment), the pain resolved after removal of the deep endometriosis nodule. It is tempting to speculate that these women had large nodules extending and attached to the ischial spine. Unfortunately, this is a clinical impression because these observations were not registered prospectively. In addition, in the more recent neuropelveologic literature, documented observations of invasion of endometriosis into large somatic nerves seem to be rare, with most cases describing endometriosis close to the nerves.

Considering neuroinflammation at a distance, and/or the hypothesis of referred pain, we suggest that it might be preferable to excise the nodule without exploration of these nerves in women with cyclic pain of large somatic nerves without clear evidence of localized nerve invasion. The surgical exploration of these nerves is technically difficult and potentially dangerous. Moreover, few surgeons have the requisite skills and experience to perform these procedures safely. Most importantly, exploration might often be unnecessary, as evidenced by frequent negative explorations and by pain symptoms that resolve after removal of the endometriosis.

In conclusion, pain caused by individual endometriosis lesions is highly variable, as is the occurrence of pain at a distance of up to 27 mm from the lesion. Clinically, this variability means that endometriosis-associated pain varies from none to very severe. Moreover, neuroinflammation at a distance is important when considering that the nerves of the pelvic wall are within 27 mm from the peritoneum with eventual endometriosis lesions. For these reasons, we consider the pathophysiology of pain at a distance from endometriosis an important observation that needs to be investigated further. Understanding why and which lesions are painful and why some are associated with pain at a distance seems important for orienting surgical decision-making, especially for observing margins during excision.

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