

Pain in the upper anterior-lateral part of the thigh in women affected by endometriosis: study of sensitive neuropathy

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Objective: To assess whether pain in the anterior-lateral part of the thigh in women affected by endometriosis is due to femoral nerve invasion by endometriotic implants.

Design: Case-control study.

Setting: Hospital.

Patient(s): We enrolled 30 patients with endometriosis and leg pain in the anterior-lateral part of the thigh and 30 healthy women.

Intervention(s): Skin biopsy and neurologic examination for detection of neuropathy.

Main Outcome Measure(s): Intraepidermal small fiber density reduction and positive neurologic examination agree with sensitive neuropathy.

Result(s): Biopsy results showed no statistically significant difference between the case group and the control group. At neurologic examination nine patients in the study group (30%) showed positive results, none in the control group showed signs. These nine patients had reduced intraepidermal small fiber density, compared to the lower cutoff values of the control group, suggesting a sensitive neuropathy.

Conclusion(s): When there is leg pain in women with endometriosis it is important to distinguish neuropathic from referred pain. Skin biopsy and neurologic examination should be introduced in the management of leg pain in endometriosis, due to their low invasiveness to diagnose a sensitive neuropathy. As a result early detection of nerve injury and planning for a prompt specific treatment would be possible. (Fertil Steril® 2013;100:122–6. ©2013 by American Society for Reproductive Medicine.)

Key Words: Endometriosis, leg pain, sensitive neuropathy, skin biopsy

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Endometriosis affects 6%–10% of women of reproductive age. It is characterized by the presence of endometrial tissue (glands and stroma) in ectopic sites, primarily the pelvic peritoneum, ovaries, and rectovaginal septum (1). Its pathogenesis is still

a matter of debate, even if many theories have been proposed: retrograde menstruation (2), celomic metaplasia (3), mullerianosis (4), stem cell origin (5), lymphatic or hematogenous dissemination (6), and genetic and immunologic predisposition (7). Endo-

metriosis symptoms are infertility, dysmenorrhea, dyspareunia, chronic pelvic pain, dysuria, dyschezia, and leg pain (1, 8). Leg pain is a symptom reported by 4% of women with chronic pelvic pain and it is statistically related to endometriosis among women with pelvic pain (8). It is estimated that 40% of women affected by endometriosis have leg pain (9). Although leg pain is a frequent endometriosis symptom that patients refer to be disabling, it is often hard to relieve because its cause is difficult to recognize. In literature

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two main causes of leg pain due to endometriosis are described: referred pain and neuropathic pain, each of which results from different locations of the endometriotic foci. Ovarian cysts (10) are generally responsible for referred pain in the medial anterior part of the thigh. Extraperitoneal implants involving the nerves play up neuropathic pain, so-called because of damage to nerve fibers. In this case pain radiates in a specific dermatome innervated by the injured nerve. Pain in the medial-anterior thigh and weakness with adduction has been described in case of endometriosis of the obturator nerve (11), whereas pain at the buttock, extending along the posterior-lateral thigh and calf to the sole of the foot is experienced in cases of endometriosis of the sciatic nerve or sciatic plexus (12). Invasion of the femoral nerve and the lateral femoral cutaneous nerve was suspected in cases of pain in the anterior and lateral part of the thigh (9). Given the extreme frequency of thigh pain among women with endometriosis, the heterogeneity of its cause and the important implications due to nerve damage (impaired sensory and motor function), it is important to find a mini-invasive method to distinguish referred pain and pain due to nerve injury. In cases of nerve infiltration endometriosis seems to lead to a small fiber neuropathy. The term small fiber neuropathy is used to describe a peripheral neuropathic process that selectively or predominantly affects unmyelinated C nerve fibers. This anatomic selectivity usually results in a clinical presentation consisting of impaired or altered pain and temperature perception with sparing of functions served by larger myelinated fibers, such as voluntary movement/strength, vibratory sensation, and proprioception (13). At present, skin biopsy is one of the most accurate diagnostic methods for small fiber neuropathies, because it permits to evaluate the density of the C nerve fiber endings, which are free in the epidermis. These fibers are reduced in case of nerve injury, because the nerve loses the regeneration capacity (13, 14). The aim of this study is to assess whether leg pain in the anterolateral region of the thigh occurring in women affected by endometriosis is due to femoral nerve invasion by endometriotic implants, as Missmer and Bove (9) have supposed. In fact this peculiar localization is rather atypical for referred pain.

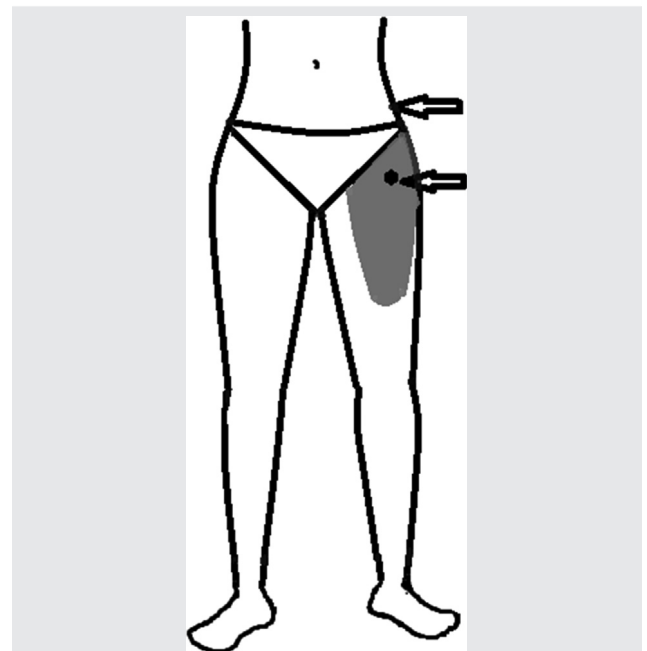
MATERIALS AND METHODS

In this case control study, conducted from May 2011 to November 2012 in S. Andrea Hospital, 30 patients were enrolled. The inclusion criteria were: age from 20–45 years, histologically confirmed endometriosis, and monolateral leg pain. We selected patients with monolateral leg pain in the anterior-lateral region of the thigh, although this is an atypical presentation of pain related to pelvic disease, because the aim of this study was to demonstrate that the pain in that unusual area was due to femoral nerve invasion by endometriosis. We also enrolled a control group, consisting of 30 women aged from 20–45 years, without symptoms (pain, infertility) and ultrasound signs of endometriosis. The exclusion criteria, for all groups, were the presence of a peripheral neuropathy or a disease that could induce it: diabetes mellitus, vasculitis, amyloidosis, alcoholism,

exposure to neurotoxic drugs, vitamin deficiencies, HIV, and hepatitis C virus infection (15).

To evaluate the presence of a peripheral neuropathy, patients underwent skin biopsy and neurologic examination. Both of these tests were conducted by experienced physicians. All patients gave their informed consent. Disinfection of area and local anesthesia with lidocaine were performed. Skin biopsy was carried out with a 3-mm punch. The biopsy was conducted in the area where pain was experienced, which corresponds to the dermatome innervated by the femoral and lateral femoral cutaneous nerves. This particular biopsy was carried out 20 cm under the anterior superior iliac spine (Fig. 1), because this is one of the two sites where a skin biopsy is performed in neurologic practice, as well as a biopsy taken 10 cm above the lateral malleolus (16). Biopsies were done by the same physician and processed following the EFNS/PNS Skin Biopsy Guideline published in 2010 (fixation in Zamboni's solution and immunoassay with polyclonal anti-protein-gene product 9.5 antibodies), to determine the linear density of intraepidermal nerve fibers (IENF) (16). After wound healing, a neurologic examination was performed. It evaluated symptoms (pain, burning dysesthesia, paresthesia, numbness, hyperesthesia, allodynia) and signs (reduction of nociceptive and tactile sensibility) of peripheral neuropathy, reflexes, muscle strength, Lasegue and Wasserman tests. All patients underwent laparoscopy to evaluate and remove endometriotic lesions. Statistical analysis was conducted using Student's *t* test. Approval by our local Ethics Committee was obtained.

FIGURE 1



The area of pain is shown in gray. The *upper* arrow indicates the anterosuperior iliac spine (landmark). The *lower* arrow shows the point where skin biopsy was performed.

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