CLINICAL REPORT

Management of Patients with Chronic Pelvic Pain Associated with Endometriosis Refractory to Conventional Treatment

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■ **Abstract:** The literature contains numerous studies on the diagnosis, pathogenesis, atypical locations, and clinical (hormonal) and surgical management of the disorder. However, no information is available on the management of endometriosis involving pain refractory to the usual treatment from the perspective of a pain unit. Our hospital has a pain unit specifically dedicated to pain in gynecology and obstetrics. The unit has been functioning since December 2005, and 52% of the attended patients have CPP of different origins. Endometriosis is present in 48% of all patients with CPP and is the most prevalent pathology in our practice. It moreover poses an important challenge in view of its enormous complexity. A descriptive study was made of the management of 44 patients with endometriosis refractory to therapy, evaluated and treated over a period of 3 years in the Pain Unit of the Maternity Center of La Paz University Hospital (Madrid, Spain). ■

Key Words: chronic pelvic pain, nerve block, neurostimulation, sacral root stimulation, endometriosis, case series

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INTRODUCTION

Endometriosis is the first cause of chronic pelvic pain (CPP) in women of child-bearing age.[1] Chronic pelvic pain is defined as nonmenstrual pelvic pain lasting over 6 months and of an intensity causing functional disability or requiring clinical or surgical treatment.[2] The estimated incidence of CPP in women of child-bearing age is 15% to 24%.[3,4] Endometriosis and adhesions are the cause of most cases of CPP in women.[5]

The treatment of CPP is particularly complicated, because it shares the features of visceral, somatic, and neuropathic pain and of both acute and chronic pain. In addition, the pelvis is an anatomical zone containing different organs, systems, and sensory and motor networks and pathways.[6] The disorder has a great impact on patient quality of life and on the psychosocial aspects of pain, because the affected individuals are typically young women, and CPP strongly interferes with aspects as important and distinct as sexual activity, micturition, or work activities. CPP thus poses a great sociosanitary problem.[7]

Endometriosis is characterized by ectopic endometrial tissue. It is a very important cause of pain and infer-

tility and may even lead to complete work disability. The etiopathogenesis remains unclear, although a number of hypotheses have been proposed: Embryonic cells may give rise to deposits in the umbilicus, while retrograde menstruation may deposit endometrial cells in the pelvis[8,9] or autoimmune disorders preventing correct elimination of the menstrual remains,[10] to genetic alterations that prevent the correct clearance of such remains.[11]

Endometriosis is diagnosed on the basis of the clinical manifestations at physical examination and requires surgical and histological confirmation.[12]

There are a range of symptoms, and women most commonly present with dysmenorrhea (painful periods) and pelvic pain, which progresses in intensity and duration over a period of months or years, and are often accompanied by dyspareunia, dyschezia, and dysuria. Unfortunately, the diagnosis is usually delayed many years.[13] Discordance between the macro- and microscopic findings and the clinical features is the rule in this disease.[12]

There have been many well-documented references to treatment in the form of nonsteroidal antiinflammatory drugs (NSAIDs), hormone therapy, laparoscopic surgery for removal of the different foci of endometriosis, hysterectomy, or laparoscopic uterosacral nerve ablation.[5,14,15] However, coadjuvant drugs, major opioids, infiltration techniques, or neurostimulation[16] are usually obviated or described only as a last management option.[2] Some authors have come to question the widespread surgical treatment of such patients and recommend a joint management approach with specialists from other fields, rather than systematically resorting to surgery.[17]

The present study describes the management of CPP associated with endometriosis from the perspective of a specialized pain unit, reporting the patients involved and the clinical, psychological, rehabilitation, and interventional treatments provided.

PATIENTS

Between December 2005 and February 2009, with IRB approval, we evaluated and treated 44 patients with CPP secondary to endometriosis referred to our service from the endometriosis unit of the hospital.

All patients had pain that was difficult to manage, defined as pain not adequately controlled with common analgesics and hormone therapy requiring strong opioid and/or invasive techniques for pain management.

Inclusion Criteria Include the Following

Endometriosis diagnosed by pathology or imaging studies highly suggestive of endometriosis, age over 18 years, ability to understand and comply with the prescribed treatment, understanding and signing an informed consent.

Exclusion Criteria Include the Following

Patients undergoing surgery for reasons other than endometriosis, associated condition that requires major opioids, infiltration techniques or neurostimulation.

Monitoring of patients and therapeutic decisions were made based on the response to drug treatment: those who responded with a perception of improvement below 30%. This perception was assessed by the question ''How much has improved over his grief over the time of initiation of treatment in our unit?'' (0 to 100%). If patients continued to maintain pain intensity greater than 5/10 on a VAS scale were subjected to infiltration techniques. If the pain relief following these techniques was adequate (VAS after procedure under 5/10) but lasted < 1 month, the patient was offered the possibility of neurostimulation techniques.

The patient series was divided into two main groups: women who had undergone surgery for endometriosis in the course of follow-up (S group) and those who had not undergone surgery (non-S group). In both groups, we studied the demographic variables, the percentage of patients treated with hormonal therapy at the first visit, the intensity of pain evaluated by the visual analog scale (VAS), the need for treatment with strong opioids, invasive techniques, or neurostimulation. Finally, we describe the current treatment and the improvement of each group.

RESULTS

The mean patient age was 38.6 years (range, 24–49), with a mean duration of follow-up of 24.06 months (range, 4–43). A full 90.1% of the patients had already undergone surgery for the diagnosis and/or treatment of endometriosis when first seen in the unit, while the remaining 9.9% underwent surgery in the course of follow-up (Figures 1 and 2).

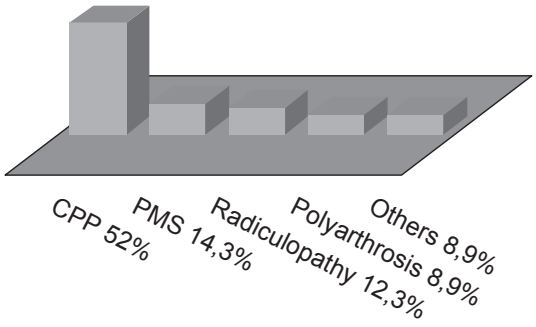

Figure 1. Patients distribution by diagnostic groups.

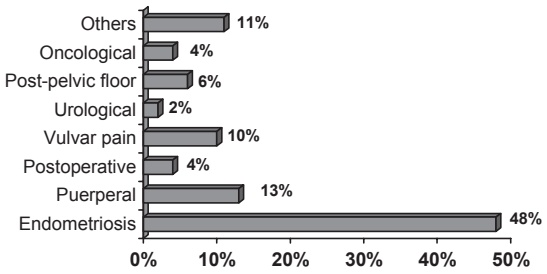

Figure 2. Chronic pelvic pain distribution.

At the time of the first visit, 59.1% of the women had received or were receiving hormone therapy as part of their treatment for endometriosis (oral contraceptives, gonadotropin releasing hormone (GnRH) analogs, or levonorgestrel-releasing intrauterine devices). All the patients made regular use of NSAIDs.

Following the anamnesis and case history, a physical examination of the pelvic zone was made—in most cases without vaginal and rectal digital exploration, because these tests were previously made in the endometriosis unit. The patients frequently reported pain in both iliac fossae, usually referred to the lumbar zones, and sometimes to the lower extremities. The distribution of pain over time was highly variable: While some patients experienced pain only a few days a month, others were only free of pain some days a month. The mean intensity of pain as assessed by the visual analog scale (VAS, recorded as the number of centimeters from the range 0 to 10—0: no pain, 10: pain as bad as possible) was high (> 7 points).

Psychological problems were very common, and the patients were referred to the service of psychiatry of the hospital for evaluation and treatment where applicable, as part of the multidisciplinary management protocol.

Therapeutic Approach

Drug Treatment. All of the patients presented referred visceral pain, almost always with a clear neuropathic component. Accordingly, our first approach to treatment involved the prescription of antidepressants (amitriptyline, mean doses 25 mg/day, duloxetine, mean doses 60 mg/day) and/or anticonvulsivants (gabapentin, mean doses 1200 mg/day, pregabalin, mean doses 300 mg/day), as well as minor opioids (tramadol, 50 mg/6 hour) as rescue medication (Figure 3).

Infiltration Techniques. The administration of local anesthetics and delayed release corticoids aims to interrupt pain transmission and lessen pain perception. When pharmacological treatment is unable to adequately control the symptoms, nerve blocks (superior and inferior hypogastric plexuses, ganglion impar)[18] or neuroaxial block techniques are used (lumbar or caudal epidural). These techniques were performed in 38.6% of our patients: caudal/lumbar epidural block: 20 patients; sympathetic blocks: 12 patients; periferical (pudendal nerve block): 4 patients. The efficacy of the epidural blocks was high but the length was limited at the time (days or weeks); a larger effect was obtained with sympathetic and periferical blocks (weeks or even months).

Only one patient received conventional radiofrequency after an impar block successful with short-term efficacy.

Neurostimulation. In some cases, the aforementioned techniques offer pain relief that is adequate but limited in terms of duration. Such patients can receive neurostimulation involving the application of an electric current to stimulate the myelinated A-beta fibers (tact), characterized by faster conduction than the nonmyelinated C fibers (pain), thereby blocking pain input.[19] Neurostimulation can be carried out in the brain cortex, thalamus, or posterior columns of the spinal cord, or at peripheral level in the vicinity of the nerves.

Neurostimulation was carried out in 11.3% of our patients. Two patients underwent bilateral transforaminal stimulation of the S3 roots, two received sacral root retrograde epidural stimulation, and one patient underwent peripheral stimulation of the right iliohypogastric and ilioinguinal nerves.

In the course of treatment in our unit, 40.9% of the patients underwent repeat surgery for endometriosis.

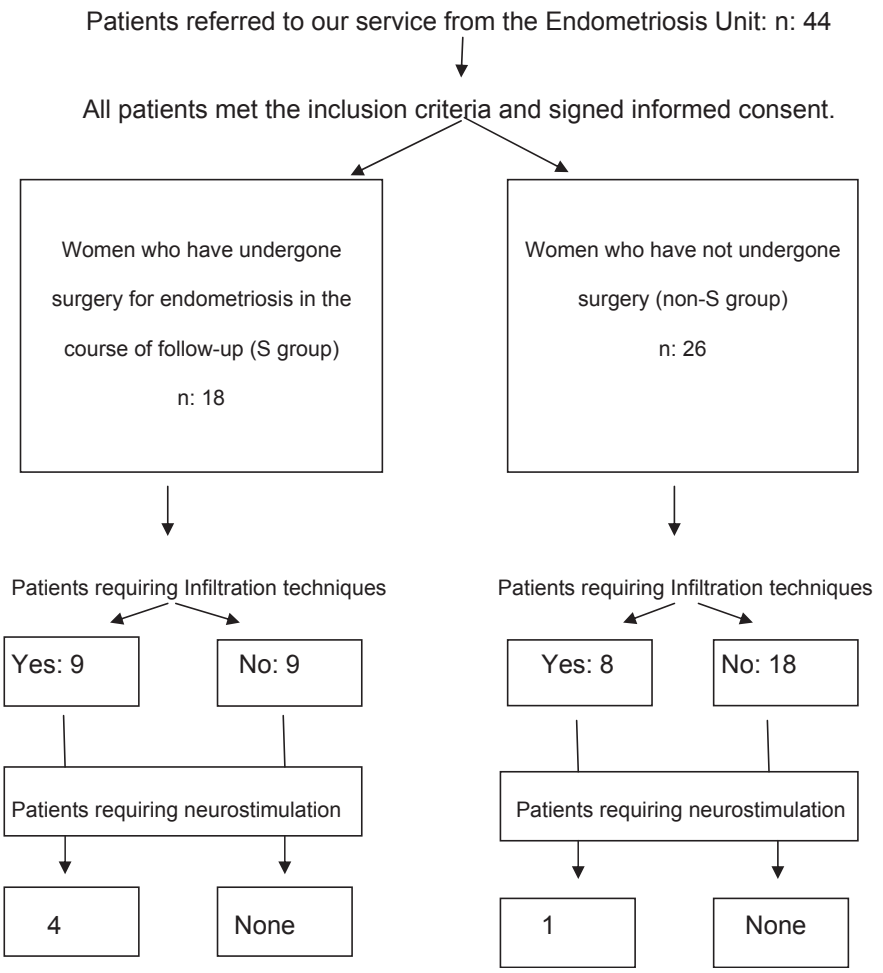

Figure 3. Flow chart studies

Current Treatment. At present, 31.8% of our patients are treated with anticonvulsivants, while 27.2% receive antidepressants. In turn, 61.3% use NSAIDs and 38.6% receive minor opioids as rescue medication, while 15.9% require major opioids (oxycodone in 6 cases and transdermal fentanyl in 1) for adequate pain control. At present, 15.09% require no treatment of any kind.

Taking into account the treatment received, overall improvement in the last 3 months vs. the first visit was recorded in 66% of the patients.

As seen in Table 1, hormone therapy at the time of the first visit is very similar in both groups. However, the need for major opioids, infiltration techniques and neurostimulation was greater in the surgical group.

Table 1. Patients Subjected to Surgery and Hormone Therapy at Time of First Visit. Third/Fourth Step Treatment Received During Follow-Up

Group	Prior Surgery	Hormone Therapy	Infiltration (Peripheral/Neuroaxial)	Major Opioid during Follow-up	NS
S	89%	44%	50%	62%	4 (22%)
(18, 41%)	(73–103%)	(21–66%)	(27–73%)	(40–85%)	(3–41%)
Non-S	92%	69%	31%	8%	1 (4%)
(26, 59%)	(81–102%)	(51–86%)	(12–47%)	(0–18%)	(0–11%)
P	0.884 (NS)	0.100 (NS)	0.197 (NS)	0.0007 ($P < 0.001$)	0.159 (NS)

Group S, previous surgery at first visit; Group Non-S, nonprevious surgery at first visit; NS, neurostimulation.
Data are expressed as absolute numbers, median (CI).

Table 2. Current Treatment and Percentage Improvement

Groups	ACs	ADs	NSAIDs	Minor Opioids	Major Opioids	Hormone Therapy	No Treatment	% Improvement	100% Improvement
S	33%	22%	55%	22%	28%	11%	16%	65%	28%
(18, 41%)	(11–55)	(3–41)	(32–78)	(3–41)	(7–48)	(3–25)	(0–34)	(43–87)	(7–48)
Non-S	31%	31%	58%	50%	8%	4%	15%	66%	38%
(26, 59%)	(13–48)	(13–49)	(39–77)	(31–69)	(0–18)	(0–11)	(1–29)	(48–84)	(20–57)
P	0.843	0.732 (NS)	0.888 (NS)	0.114 (NS)	0.110 (NS)	0.558 (NS)	0.760 (NS)	0.929 (NS)	0.531 (NS)

Group S, previous surgery at first visit; Group Non-S, nonprevious surgery at first visit; ACs, anticonvulsivants; ADs, antidepressants.
Data are expressed as median (CI).

Table 2 shows the type of clinical treatment currently administered to our series of patients. Percentage improvement is also shown. Of note is the greater need for major opioids and neurostimulation techniques in the patients subjected to surgery in the course of follow-up. A portion of patients report 100% improvement, and approximately 15% of the women presently require no medication of any kind.

In relation to the patients requiring neurostimulation, the overall improvement rate was 66.7%. One patient with transforaminal S3 stimulation and another with retrograde sacral stimulation are currently undergoing a ganglion impar infiltration cycle for residual perineal pain. One patient with transforaminal S3 stimulation has requested the removal of the electrodes for performance of a magnetic resonance imaging scan, despite the fact that neurostimulation proved effective in this case. The patient subjected to subcutaneous peripheral stimulation lost paresthesia and clinical improvement—as a result of which the electrodes were removed.

The other three patients maintain improvement in excess of 50% after 4 years.

DISCUSSION

Chronic pelvic pain (CPP) secondary to endometriosis represents a challenge for pain units. The mechanisms underlying pain in this disease are still unclear,[20] and the presence within the pelvic space of numerous anatomical structures complicates the management of such patients. The complexity of neural anatomy in the pelvic zone and the singularity of visceral pain (originating in free nerve endings and transmitted by nonmyelinated or poorly myelinated fibers closely associated with somatic nociception) facilitate viscero-visceral and visceral-somatic convergence.[21] This results in that these patients referred a generalized pelvic pain although it may be that not such organs are directly involved. As a result of these characteristics, the patients present gynecological, urinary and intestinal manifestations, referred somatic pain (in some cases with associated muscle contractures), and very often also neuropathic pain secondary to the damage of nerve structures as an original consequence of the disease, or as a result of surgery.

This complexity of the nociceptive pathways in turn offers a treatment alternative, because neuromodulation (both chemical in the form of nerve block and electrical in the form of neurostimulation) offers treatment possibilities when the classical therapies used for endometriosis (hormone therapy, surgery) are unable to secure adequate pain control.

In our series, 66% of the patients claimed to have experienced improvement at the time of their first visit to our unit. In this context, improvement rates of over 30% in chronic pain are taken to represent a good result.[22] This evaluation on the part of the patients refers not only to the intensity of pain but also to overall quality of life (physical, sexual, emotional, occupational, family, etc.). Based on these results, the mean improvement is at least 40% in both groups and appear to reflect at least moderate clinically important differences.[23]

A total of 38.6% of the women underwent some type of block at some point during follow-up. This treatment might allow improved pain control and a lesser need for oral medication.

In any case, a large percentage of our patients (40.9%) underwent repeat surgery in the course of follow-up. Although it was not the objective of our study to evaluate surgery in the control of the pain symptoms, the women who underwent surgery were seen to require a larger number of infiltration techniques (50% vs. 30.7% among the nonsurgical patients), with a greater consumption of major opioids (27.7% vs. 7.6%), and a more frequent need for neurostimulation (22.2% vs. 3.8%)—even in the presence of similar starting or baseline pain.

CONCLUSIONS

No large series have examined endometriosis-related chronic pelvic pain (CPP) and its treatment from the perspective of a pain unit. The management of such patients is complex because of the particular characteristics of the causal disorder and the anatomical and neurological configuration of the pelvic space.[20,21]

Clinical management (anticonvulsivants, antidepressants, opioids) allows adequate pain control in approximately one-half of all patients with CPP secondary to endometriosis refractory to conventional treatment. CPP can be treated with nerve blocks and drugs, with overall results comparable to those obtained in patients subjected to surgery. In concordance with other authors,[17] we consider that infiltration and neuromodulation techniques are adequate options for patients with CPP secondary to endometriosis refractory to conventional treatment and may contribute to the avoidance of the morbidity–mortality associated with surgery, which does not always afford clinical benefit.

LIMITATIONS OF THE STUDY

We did not perform a statistical comparison between two types of treatment. We divided the patients into two groups to explain the evolution of pain and treatments with no aim other than to suggest the differences between them.

Prospective, randomized, controlled studies are needed to assess the true efficacy of all the therapeutic options, although the complexity of the disease, its clinical variability, and its enormous psychosocial impact make such studies very difficult to carry out.

REFERENCES

1. Milingos S, Protopapas A, Kallipolitis G, et al. Endometriosis in patients with chronic pelvic pain: is staging predictive of the efficacy of laparoscopic surgery in pain relief? *Gynecol Obstet Invest*. 2006;62:48–54.

2. Howard FM. Chronic pelvic pain. *Obstet Gynecol*. 2003;101:594–611.

3. Mathias SD, Kuppermann M, Liberman RF, Lipschutz RC, Steege JF. Chronic pelvic pain: prevalence, health-related quality of life, and economic correlates. *Obstet Gynecol*. 1996;87:321–327.

4. Zondervan KT, Yudkin PL, Vessey MP, et al. The community prevalence of chronic pelvic pain in women and associated illness behaviour. *Br J Gen Pract*. 2001;51: 541–547.

5. Gelbaya TA, El-Halwagy HE. Focus on primary care: chronic pelvic pain in women. *Obstet Gynecol Surv*. 2001;56:757–764.

6. Jarrell J. Demonstration of cutaneous allodynia in association with chronic pelvic pain. *J Vis Exp*. 2009;28:1232.

7. Cheong Y, William Stones R. Chronic pelvic pain: aetiology and therapy. *Best Pract Res Clin Obstet Gynaecol*. 2006;20:695–711.

8. Sampson J. The development of the implantation theory for the origin of peritoneal endometriosis. *Am J Obstet Gynecol*. 1940;40:549–556.

9. Batt RE, Smith RA. Embryologic theory of histogenesis of endometriosis in peritoneal pockets. *Obstet Gynecol Clin North Am*. 1989;16:15–28.

10. Sinaii N, Cleary SD, Ballweg ML, Nieman LK, Stratton P. High rates of autoimmune and endocrine disorders, fibromyalgia, chronic fatigue syndrome and atopic diseases among women with endometriosis: a survey analysis. *Hum Reprod*. 2002;17:2715–2724.

11. Bischoff F, Simpson JL. Genetic basis of endometriosis. *Ann N Y Acad Sci*. 2004;1034:284–299.

12. Ballard K, Lane H, Hudelist G, Banerjee S, Wright J. Can specific pain symptoms help in the diagnosis of endometriosis? A cohort study of women with chronic pelvic pain *Fertil Steril*. 2010;94:20–27.

13. Ballweg ML. Big picture of endometriosis helps provide guidance on approach to teens: comparative historical data show endo starting younger, is more severe. *J Pediatr Adolesc Gynecol*. 2003;16:S21–S26.

14. Solnik MJ. Chronic pelvic pain and endometriosis in adolescents. *Curr Opin Obstet Gynecol*. 2006;18:511–518.

15. Gunter J. Chronic pelvis pain: an integrated approach to diagnosis and Treatment. *Gynecol Surv*. 2003;58:615–623.

16. Al Tamimi M, Davids R, Barolat G, Krutsch J, Ford T. Subcutaneous peripheral nerve stimulation treatment for chronic pelvic pain. *Neuromodulation*. 2008;11:277–281.

17. Butrick CW. Chronic pelvic pain: how many surgeries are enough? *Clin Obstet Gynecol*. 2007;50:412–424.

18. Patt R, Plancarte R et al. Superior hypogastric plexus block. A new therapeutic approach for pelvic pain. Chapter 36. Interventional Pain Management (Wallman and Winnie), pages: 384–391.

19. Melzak R. From the gate to the neuromatrix. *Pain*. 1999; (suppl 6):S121–126.

20. Lamvu G, Steege JF. The anatomy and neurophysiology of pelvic pain. *J Minim Invasive Gynecol*. 2006;13:516–522.

21. Malykhina AP. Neural mechanisms of pelvic organ cross-sensitization. *Neuroscience*. 2007;149:660–672.

22. Dworkin RH, Backonja M, Rowbotham MC, et al. Advances in neuropathic pain: diagnosis, mechanisms, and treatment recommendations. *Arch Neurol*. 2003;6011:1524–1534.

23. Dworkin RH, Turk DC, Wyrwich KW. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. *J Pain*. 2008;9:105–121.