JOURNAL of ANESTHESIA and PERIOPERATIVE MEDICINE

Review Article

Chronic Sciatica Induced by Endometriosis

Sisi Chen

ABSTRACT

Aim of review: Endometriosis is known as a chronic disease in which endometrial stromal and glandular cells appear outside the uterus cavity, causing mainly infertility and chronic pain. Endometriosis of sciatic nerve is uncommon and can cause severe sciatica, with the mechanisms not clearly recognized. Along with the physical symptoms, there might be psychological issues in women who have endometriosis. Understanding the interaction between the endometriotic lesions and the nervous system will help to improve the current diagnosis and the effective management of sciatic endometriosis.

Methods: As we know that the pathogenesis of endometriosis mainly refers to inflammation and neuropathy, which brings out some study bases of endometriosis-induced sciatica. First, this review focused on the development of sciatic endometriosis as well as reporting related clinical cases of patients who had sciatic endometriosis; second, we narrated the main symptom of sciatic endometriosis, which is chronic sciatica, and its potential mechanisms; finally, we discussed the existing diagnosing theory and management with the hope of exploring better strategies for future references.

Recent findings: Diagnosis always can be made by magnetic resonance imaging (MRI) and surgical gross findings with histopathological examinations. The findings that endometrial-like tissue can develop at the sciatic nerve, offer new insights for better understanding and treating sciatic endometriosis. Many studies have reported that the symptoms could be alleviated by surgically removing the endometriotic lesions. New evidence showed that in a rat model, sciatic endometriosis could cause neuropathic pain and local inflammation.

Summary: This article is aimed to review reports about chronic sciatica induced by endometriosis, explore the possible mechanisms and come up with effective treatments.(Funded by the National Institutes of Health.)

From the Pain Research Center, Department of Anesthesiology, University of Cincinnati College of Medicine, Cincinnati, OH, USA.

Correspondence to Dr. Sisi Chen at sisi.chen@uc.edu.

Citation: **Sisi Chen. Chronic Sciatica Induced by Endometriosis. *J Anesth Perioper Med* 2018;5:325-332.**

doi: **10.24015/JAPM.2018.0113**

Endometriosis is defined as a gynecological condition in which cells from the lining of the uterus (endometrium) appear and flourish outside the uterine cavity, affecting approximately 10% of women in reproductive age – around 30's, which is uncommon in the under-20's (1). However, it can be difficult to estimate the prevalence of endometriosis due to the individually-different symptoms and the diversity of severity, and sometimes endometriosis can even be asymptomatic (2).

Chronic pain, as a primary condition which causes comorbidity and disability, is one of the major problems caused by endometriosis. Among all the pain symptoms, chronic sciatica is more and more being the complaint by patients who suffer from endometriosis. The causing of chronic sciatica is mainly due to endometriosis tissue are often found on or around sciatic nerve (sciatic endometriosis). The correct diagnosis of sciatic endometriosis is at a high risk of being missed due to the lack of recognition of this disease. When endometriosis lesions are present at the site of the sciatic nerve, neuropathic pain, nociceptive pain and inflammatory pain will develop. In this review, we will discuss the existing studies to understand the potential mechanisms of sciatic endometriosis, as well as to explore more efficient diagnostic methods and treatments.

Like most of the other diseases, the development of endometriosis needs both genetic and environmental factors. Among all the potential risk factors (Table 1), genetic factors make the 51% contribution to endometriosis risk. As early as in 1980's, there was a report about a six-fold risk of endometriosis in sisters of affected women (3). Changes in chromosome 10 at region 10q26 and chromosome 7 at region 7p15.2 may cause the development of endometriosis (4,5). A higher likelihood of endometriosis may due to women with early menarche, short and heavy menstrual cycles, and an early history of dysmenorrhea (4, 6). Between an increased risk of endometriosis and smoking, alcohol, a fat-rich diet, and less physical activity, the relationship has been discussed in several studies (7, 8).

Pathophysiology and Pathogenesis

Retrograde menstruation, coelomic metaplasia and embryonic cell rests have been presented as the most reasonable hypotheses of pathogenesis of endometriosis (9), with retrograde menstruation phenomenon being the most well-accepted theory (1, 10). For peritoneal endometriosis implants, it is generally considered to be implanted after endometrium fragments flow into peritoneal cavity along with retrograde mense (11, 12, 13). Referring to endometriosis of the sciatic nerve, a highly acknowledged concept is about an anatomic sign which was first described by Head as "pocket sign" – a peritoneal invagination, downward toward the greater sciatic notch, in the posterior part of the pelvis (14). The first case of endometriosis-induced sciatica was described by Schlincke in 1946 (15). There are two types of endometriosis of the sciatic nerve basically – deep infiltrating endometriosis of the rectovaginal septum with the involvement of the sciatic nerve roots, which can be seen as endopelvic endometriosis, and isolated endometriosis of the sciatic nerve. Some endometrial foci were found within the sciatic nerve itself – under the sheath, which is one of the rarest variations of the condition (16).

Endometriosis is also considered as a disease with dysfunction immune system. It was reported that endotoxin (LPS), a potential inflammatory mediator, concentration in menstrual fluid (MF) / peritoneal fluid (PF) was significantly higher in women with endometriosis than those without endometriosis. The elevated LPS promoted the growth of endometriotic cells at the ectopic site, contributing the development and maintenance of endometriosis (17). In endometrial lesions, infiltrating macrophages was considered as a consistent feature. With the activation of macrophages, a large amount of vascular endothelial growth factor (VEGF) was generated and initiated neovascularization in the new tissue (18).

Pain Symptoms

Symptoms of endometriosis are often described as infertility and chronic pain. The most essential problem is chronic pain, which can occur unpredictably, be related to the menstrual cycle or even continuous (1). Most of the endometriosis patients suffer from chronic pelvic pain (dysmenorrhea, chronic pelvic pain, dyspareunia – painful sexual intercourse, dysuria – painful urina-

tion, dyschezia – painful defecation, et al.). Of patients who have endometriosis of the sciatic nerve, lesions of the ipsilateral sciatic nerve are reported as the primary cause of almost all the endometriosis-induced cyclic sciatica (9). Some case reports showed that those reproductive-age women with catamenial sciatica-like pain should consider sciatic nerve endometriosis and which were verified by histology and pathology as sciatic endometriosis. Cyclic sciatica caused by biopsy-proven endometriosis was first described in 1955 (19). Catamenial pain, weakness and sensory loss are presented as the most frequent symptoms of endometriosis of the sciatic, femoral or lumbosacral nerve roots (20).

It is estimated that 40% of women affected by endometriosis have leg pain, mostly cyclic sciatica-like pain appearing along with menstruation – catamenial sciatica-like pain with normal CT or MRI of the spine (21). Sciatica is traditionally defined as pain along the distribution areas of the sciatic nerve. Combined by L4, L5, S1, S2 and S3, the roots of sciatic nerve exit the spinal cord. Endometriosis lesions either form around the five roots or directly involve the peripheral sciatic nerve can cause irritation, which leads to sciatica. Due to the property of endometriosis as estrogen-dependent (22), this kind of sciatica is cyclic and catamenial, and it is considered as referred pain (23) and neuropathic pain (24, 25, 16), with the latter one thought by clinical doctors and researchers as endometrial foci is found around peripheral nerves and causes inflammation or damage to the nerves. Some researchers think most cyclic leg pain is referred, with endometrial lesions locating at posterolateral pelvic peritoneum irritate the roots of the sciatic nerve (23).

Having much likeliness with endometriosis of the bladder or bowel, endometriosis lesions involve the sciatic nerve are highly destructive which cause dysfunction of the sciatic nerve. Patients often complain having thigh pain even down to the posterior or lateral aspect of the calf to the foot, sometimes along with sensory loss, muscle weakness, and reflex alterations (26), depending on the extent of sciatic nerve damage. Also, women with sciatica are usually sent to orthopedic or neurology departments, causing the delay of diagnosis (27). Thus, we should pay much more attention to this kind of disease that is hard to diagnose and easy to be neglected (28), and come up with effective treatment plans before the damage becomes irreversible.

Table 1. The Development of Endometriosis is Contributed by Multiple Risk Factors.

Genetics (51%)
Family history
Individual genomic changes
Menstrual and reproductive issues
Early menarche, short and heavy menstrual cycle (↑)
Early history of dysmenorrhea (↑)
Others
Smoking, alcohol consumption, and a diet with rich saturated fat (↑)
Lower body mass index (↓)
Regular physical activity (↓)

The table demonstrated the possible contributors for endometriosis in general. An increase in genetic mutation or a history of endometriosis in family members, a history of menstrual issues and other factors like smoking and alcohol consumption can also cause the development of endometriosis. The risk is presented as the direction of the arrow (upward=increase of risk; downward=decrease of risk).

Pain Mechanisms

Several mechanisms of pain in endometriosis have been described as inflammatory, nociceptive or neuropathic mechanisms, and there is evidence that all three of these mechanisms are relevant to pelvic pain that endometriosis-associated (Figure 1) (29).

For intrapelvic endometriosis, endometrial fragments which shed into the pelvic cavity adhere to the peritoneal surface, sometimes even invade into the abdominal wall, causing local and systematic inflammation, which can lead to unpredictable, catamenial or continuous pain. Several serum protein markers like c-reactive protein (CRP) and serum amyloid A (SAA) have already been found increasing in some patients have stage III and IV endometriosis (30). There is a wide-accepted theory of the etiology of endometriosis is dysfunction of immune cells, which is studied mostly in peritoneal fluid (31, 32). With nature killer (NK) cells' defect activity and a decreased cytotoxicity to endometrial cells, it is thought to promote implantation of endometrial tissue as a tissue graft (33). It has

been shown that there is an increased level of inflammatory cytokines in peritoneal fluid of endometriosis patients, like interleukin (IL)-1, IL-6, IL-8, tumor necrosis factor-α, transforming growth factor-β and monocyte chemotactic protein (MCP)-1 (34,35). The most recent finding is ectopic endometrium-derived leptin produces estrogen-dependent chronic pain (36). Overproduced cytokines, chemokines and prostaglandins were found to be associated with pain in endometriosis (37-42), in which macrophages play an important role (43-45).

Nociceptive pain includes 4 basic steps – transduction, transmission, modulation and perception (27). The nerves that primarily consider as nociceptors are C and Aδ fibers. Endometriotic foci were found innervated mainly by sensory C and sensory Aδ, which can be nociceptors for noxious stimuli – endometriotic lesions (46). There are also studies verify that sensory and sympathetic nerves invade the ectopic endometrial tissue both in rat model (47) and in human researches (48-52). The ectopic foci can develop sensory and sympathetic nerve supply, connecting itself with the central nervous system. Chen et al. found that when autologous uterus tissue was implanted onto sciatic nerve of rat established sciatic endometriosis and caused pain and local inflammation, and by surgically removing the endometriosis lesion could reverse the pain-like symptoms (53). Some clinical studies also showed that after surgically remove the foci, there was obvious alleviation of pain (54,55).

Neuropathic pain is pain produced by damage to or dysfunction of neurons in the peripheral or central nervous system. Growth-associated protein (GAP)-43 is a marker molecule for neural outgrowth and regeneration, which is moderately to strongly expressed in endometriosis-associated nerve fibers, supporting the possibility of neuropathic pain (56). In rectovaginal septum endometriotic nodules, a high proportion of the nerves are found, and there is a significant correlation between nerves and ectopic endometrium tissue, which may invade the nerve perineurially (47). Sometimes endometriosis patients feel an increased level of pain due to central sensitization but not peripheral nerves damage (48,57).

With the many possible causes of leg pain in women with endometriosis, it is unknown that if it's due to one or more peripheral nerve directly affected or co-existing pathologies (21). Sometimes intrapelvic inflammatory endometrioma – especially deep infiltrating endometriosis of the rectovaginal septum can affect the nerve and axon nearby – like a neuritis, and cause leg pain (58). Assume that cytokines produced by inflammation of endometriosis lesion can also irritate nearby nerves as nociceptive pain generators. During each menstrual cycle, with ectopic endometrium cells affected by level changes of estrogen and progesterone, foci in or around the sciatic nerve undergoes hemorrhage into the surrounding tissues and can cause considerable inflammation (16). However, there are few reports about mechanisms how lesions directly involve the peripheral sciatic nerve outside the pelvic cavity causing leg pain. Chen et al. (53) found that sciatic endometriosis caused robust local inflammation and sciatic nerve damage at the affected area, which contributed to sciatica. There were elevated pro-inflammatory cytokines at the ectopic site. The local inflammation and the compression from the endometrial cyst caused nerve damage, and then induced neuropathic pain. At the same time, the inflammatory cytokines could be stimulators damaging the surrounding tissues and cause nociceptive pain. However, there was no evidence of newly grown nerve fibers in the endometrial cyst tissue.

Moreover, it is well-accepted that changes in the central nervous system also contribute to chronic pain in endometriosis patients (59, 60). However, there is a lack of further studies regarding sciatic endometriosis specifically.

Diagnosis and Management

Diagnosis often relies on typical sciatica beginning just a few days before menstrual cycles and lasting almost the whole menses, with no low back pain experienced. With the hemorrhage of endometrium-like tissue going on, the MRI can be presented as a specific diagnosis of sciatic endometriosis and is recommended for evaluation of endometriosis-induced sciatica when the pain level appears differently during the menstrual cycle or with patients who have a history of endometriosis (61). MRI findings of sciatic nerve endometriosis are mostly described as a mixed sig-

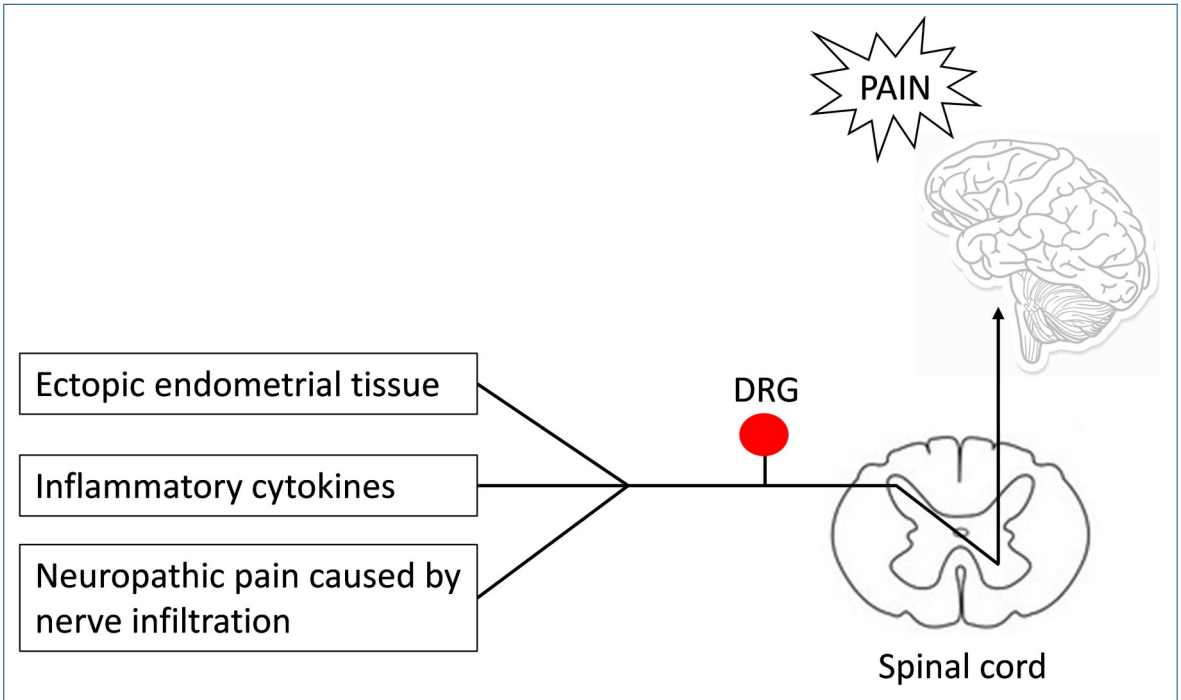

Figure 1. Endometrial Tissue Itself as a Nociceptive Stimulator, the Inflammatory Response and Neuropathic Changes Cause Pain.
Endometriotic lesions with cyclic hemorrhage inside of the cysts can be noxious stimuli which activate the surrounding nociceptors. Increased level of inflammatory cytokines was found in the peritoneal fluid of endometriosis patients and the site of ectopic endometrial lesions. The lesions also cause constriction and infiltration of the affected nerve which further induces neuropathic pain.

nal(s) in the sciatic nerve – usually between the sciatic notch and greater trochanter, with hemorrhage within the mass. Lesions can be surgically removed during surgical exploration, then proved as endometrial tissues histologically and pathologically.

Management of endometriosis mainly includes treatment for infertility and treatment for chronic pain (Figure 2). Both medical and surgical approaches can be used in women with endometriosis. Medical therapy can always be an essential part of this estrogen-dependent disease, for instance, GnRH agonists, danazol, gestrinone, and oral contraceptives and progestins. The goal is to achieve a respectively stable hormone milieu and to reduce the endometrial cells proliferation. In the USA, most patients receive a surgical treatment within the first year of diagnosis. Associated with chronic pain and infertility (1), to treat those patients and maintain life quality is costly (US$706 per month) (62).

Treatment for infertility can be divided into two parts. One is surgically removing ectopic endometrium tissue and to resume the normal relationships of pelvic organs. The other one is overlooking the abnormal pelvic environment and perform in vitro fertilization (IVF), which retrieve oocytes directly from the ovaries and place the embryo in the uterine cavity (22). Also, in cases of endometriosis of the sciatic nerve, conservative surgery which only removes endometrium tissue from the nerve can be successful for whom want to keep reproductive function (63). However, medical treatment has no effect on infertility in women with endometriosis (22). For pain management, GnRH-agonist has been studied more than other medical treatments (64). Recent studies show that without postoperative hormonal therapy, recurrence of pain symptoms is becoming what puzzle both doctors and patients

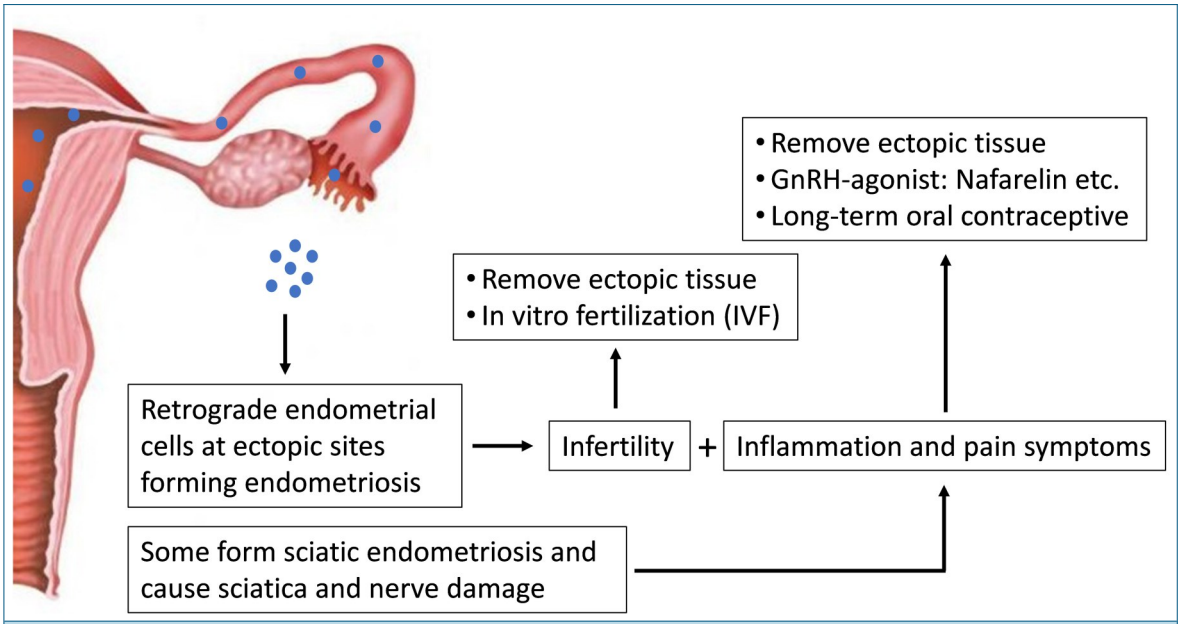

Figure 2. Retrograde Endometrial Tissues Adhere to Ectopic Sites and Form Endometriosis. Endometriosis causes both infertility and chronic pain. Specifically, sciatic endometriosis causes cyclic or ongoing sciatica due to local inflammation and/or nerve damage induced by ectopic endometrium infiltration. Current treatments regarding the symptoms of endometriosis focus on surgically removing ectopic tissue, which can treat most cases of endometriosis, and IVF for infertility or medication for pain management.

the most (65). Sometimes pain recurs without lesions grow back. Nafarelin, a GnRH agonist, using 6 months after surgical treatment, can delay the recurrence of pain symptoms (66). According to some research findings, long-term oral contraceptive pills can reduce the recurrent of pain induced by endometriosis (67).

It is often difficult to assess the efficacy of both medical and surgical treatments. There is also no significant superiority of one over the other. However, since different endometriosis patients might possess different types of pain, there is evidence that medical treatment is sometimes preferable in specific cases. For example, GnRH agonist was found more effective than oral contraceptives targeting dysmenorrhea (68). A prospective study with 2-5 years follow-up showed that a majority of endometriosis patients benefitted from laparoscopic excision surgeries, and only 36% of them would require further surgery because of recurrence of endometriosis which was confirmed histologically (69). Taken the recurrence of endometriosis into consideration, it is necessary to combine medical treatment after an excision surgery as a long-term plan. It has shown that six months of GnRH application after laparoscopic surgery generated a greater relief from endometriosis-induced pain and a delay of a necessity of further treatment (70).

Brought out are also psychosocial consequences as depression, anxiety, decreased quality of life and work efficiency (71,72), which can't be ignored and should be treated as well. Endometriosis, as a chronic condition, often negatively affects patients intimate relationships as well (73). More commonly, researchers have found out endometriosis has a huge impact on patients working lives. Generally, women who are diagnosed as endometriosis have an average of 13% loss of work time, and the economic burden associated with treating endometriosis can be extremely high and comparable to other comorbidities with chronic nature (74). At last, endometriosis is also associated with higher rates of depression, anxi-

ety and emotional distress (74,75).

Conclusions

In a nutshell, great progress has been made in recognizing, diagnosing and treating endometriosis (76, 77). As early as in 1980, rabbits were used to perform autologous transplant to induce endometriosis (78), with also hamsters (79) and rats (80, 53). Lots of studies have been focusing on using animal models to get to know better about endometriosis. However, for endometriosis of the sciatic nerve, the development, pathogenesis, pain mechanisms, and treatments are still not fully-known, let alone well-practiced in clinical use. In the future study, new animal models of sciatic endometriosis should be established, so that researchers can dig into the mechanisms and come up with better, even more, individual treatment plans. In this regard, more efforts need to be made, both theoretical knowledge and clinical approaches, aiming at pain relief, reproductive ability regaining, and reducing expenditure on health care.

This study was supported in part by grants (NS045594, NS055860, and AR068989) from the National Institutes of Health.

The authors declare no conflicts of interest.

References

1. Giudice LC. Clinical practice. Endometriosis. *N Engl J Med* 2010; 362(25): 2389-98.
2. Engemise S, Gordon C, Konje JC. Endometriosis. *BMJ* 2010; 340:c2168.
3. Lamb K, Hoffmann RG, Nichols TR. Family trait analysis: a case-control study of 43 women with endometriosis and their best friends. *Am J Obstet Gynecol* 1986; 154(3): 596-601.
4. Treloar SA, Bell TA, Nagle CM, Purdie DM, Green AC. Early menstrual characteristics associated with subsequent diagnosis of endometriosis. *Am J Obstet Gynecol* 2010; 202(6): 534.e1-6.
5. Painter JN, Anderson CA, Nyholt DR, Macgregor S, Lin J, Lee SH, et al. Genome-wide association study identifies a locus at 7p15.2 associated with endometriosis. *Nat Genet* 2010; 43(1): 51-4.
6. Darrow SL, Vena JE, Batt RE, Zielezny MA, Michalek AM, Selman S. Menstrual cycle characteristics and the risk of endometriosis. *Epidemiology* 1993; 4 (2): 135-42.
7. Parazzini F, Chiaffarino F, Surace M, Chatenoud L, Cipriani S, Chiantera V, et al. Selected food intake and risk of endometriosis. *Hum Reprod* 2004; 19(8): 1755-9.
8. Parazzini F, Cipriani S, Bravi F, Pelucchi C, Chiaffarino F, Ricci E, et al. A metaanalysis on alcohol consumption and risk of endometriosis. *Am J Obstet Gynecol* 2013; 209(2): 106.e1-10.
9. Vercellini P, Chapron C, Fedele L, Frontino G, Zaina B, Crosignani PG. Evidence for asymmetric distribution of sciatic nerve endometriosis. *Obstet Gynecol* 2003; 102(2): 383-7.
10. Burney RO, Giudice LC. Pathogenesis and pathophysiology of endometriosis. *Fertil Steril* 2012;98(3): 511-9.
11. Witz CA, Monotoya-Rodriguez IA, Schenken RS. Whole explants of peritoneum and endometrium: a novel model of the early endometriosis lesion. *Fertil Steril* 1999; 71(1): 56-60.
12. Witz CA, Thomas MR, Montoya-Rodriguez IA, Nair AS, Centonze VE, Schenken RS. Short-term culture of peritoneum explants confirms attachment of endometrium to intact peritoneal mesothelium. *Fertil Steril* 2001; 75(2): 385-90.
13. Groothuis PG, Koks CA, de Goeij AF, Dunselman GA, Arends JW, Evers JL. Adhesion of human endometrial fragments to peritoneum in vitro. *Fertil Steril* 1999; 71(6): 1119-24.
14. Head HB, Welch JS, Mussey E, Espinosa RE. Cyclic sciatica. Report of case with introduction of a new surgical sign. *JAMA* 1962; 180: 521-4.
15. Schlicke CP. Ectopic endometrial tissue in the thigh. *J Am Med Assoc* 1946; 132: 445.
16. Mannan K, Altaf F, Maniar S, Tirabosco R, Sinisi M, Carlstedt T. Cyclical sciatica: endometriosis of the sciatic nerve. *J Bone Joint Surg Br* 2008; 90(1): 98-101.
17. Khan KN, Kitajima M, Hiraki K, Yamaguchi N, Katamine S, Matsuyama T, et al. Escherichia coli contamination of menstrual blood and effect of bacterial endotoxin on endometriosis. *Fertil Steril* 2010; 94(7): 2860-3
18. Martinez FO, Sica A, Mantovani A, Locati M. Macrophage activation and polarization. *Front Biosci* 2008;13:453-61.
19. Denton RO, Sherrill JD. Sciatic syndrome due to endometriosis of sciatic nerve. *South Med J* 1955; 48 (10): 1027-31.
20. Zager EL, Pfeifer SM, Brown MJ, Torosian MH, Hackney DB. Catamenial mononeuropathy and radiculopathy: a treatable neuropathic disorder. *J Neurosurg* 1998; 88(5): 827-30.
21. Missmer SA, Bove GM. A pilot study of the prevalence of leg pain among women with endometriosis. *J Bodyw Mov Ther* 2011; 15(3): 304-8.
22. Vercellini P, Viganò P, Somigliana E, Fedele L. Endometriosis: pathogenesis and treatment. *Nat Rev Endocrinol* 2014;10(5):261-75.
23. Vilos GA, Vilos AW, Haebe JJ. Laparoscopic findings, management, histopathology, and outcome of 25 women with cyclic leg pain. *J Am Assoc Gynecol Laparosc* 2002; 9(2): 145-51.
24. Baker GS, Parsons WR, Welch JS. Endometriosis within the sheath of the sciatic nerve. Report of two patients with progressive paralysis. *J Neurosurg* 1966; 25(6): 652-5.
25. Yekeler E, Kumbasar B, Tunaci A, Barman A, Bengisu E, Yavuz E, et al. Cyclic sciatica caused by infiltrative endometriosis: MRI findings. *Skeletal Radiol* 2004;33(3):165-8.
26. Moeser P, Donofrio PD, Karstaedt N, Bechtold R, Greiss FC Jr. MRI findings of sciatic endometriosis. *Clin Imaging* 1990; 14(1): 64-6.
27. Possover M, Schneider T, Henle KP. Laparoscopic therapy for endometriosis and vascular entrapment of sacral plexus. *Fertil Steril* 2011; 95(2): 756-8.
28. Possover M, Chiantera V. Isolated infiltrative endometriosis of the sciatic nerve: a report of three patients. *Fertil Steril* 2007;87(2):417.e17-9.
29. Howard FM. Endometriosis and mechanisms of pelvic pain. *J Minim Invasive Gynecol* 2009; 16(5): 540-50.
30. Abrao MS, Podgaec S, Filho BM, Ramos LO, Pinotti JA, de Oliveira RM. The use of biochemical markers in the diagnosis of pelvic endometriosis. *Hum Reprod* 1997; 12(11): 2523-7.
31. Braun DP, Gebel H, House R, Rana N, Dmowski NP. Spontaneous and induced synthesis of cytokines by peripheral blood monocytes in patients with endometriosis. *Fertil Steril* 1996; 65(6): 1125-9.
32. Ho HN, Wu MY, Yang YS. Peritoneal cellular immunity and endometriosis. *Am J Reprod Immunol* 1997; 38(6): 400-12.
33. Bartosik D, Jacobs SL, Kelly LJ. Endometrial tissue in peritoneal fluid. *Fertil Steril* 1986; 46(5): 796-800.
34. Pizzo A, Salmeri FM, Ardita FV, Sofo V, Tripepi M, Marsico S. Behaviour of cytokine levels in serum and peritoneal fluid of women with endometriosis. *Gynecol Obstet Invest* 2002; 54(2): 82-7.
35. Kalu E, Sumar N, Giannopoulos T, Patel P, Croucher C, Sherriff E, et al. Cytokine profiles in serum and peritoneal fluid from infertile women with and without endometriosis. *J Obstet Gynaecol Res* 2007; 33(4): 490-5.
36. Alvarez P, Bogen O, Chen X, Giudice LC, Levine JD. Ectopic endometrium-derived leptin produces estrogen-dependent chronic pain in a rat model of endometriosis. *Neuroscience* 2014; 258: 111-20.
37. Hornung D, Ryan IP, Chao VA, Vigne JL, Schriock ED, Taylor RN. Immunolocalization and regulation of the chemokine RANTES in human endometrial and endometriosis tissues and cells. *J Clin Endocrinol Metab* 1997; 82(5): 1621-8.
38. Chung HW, Wen Y, Chun SH, Nezhat C, Woo BH, Lake Polan M. Matrix metalloproteinase-9 and tissue inhibitor of metalloproteinase-3 mRNA expression in ectopic and eutopic endometrium in women with endometriosis: a rationale for endometriotic invasiveness. *Fertil Steril* 2001; 75(1): 152-9.
39. Chung HW, Lee JY, Moon HS, Hur SE, Park MH, Wen Y, et al. Matrix metalloproteinase-2, membranous type 1 matrix metalloproteinase, and tissue inhibitor of metalloproteinase-2 expression in ectopic and eutopic endometrium. *Fertil Steril* 2002; 78(4): 787-95.
40. Reis FM, Petraglia F, Taylor RN. Endometriosis:

hormone regulation and clinical consequences of chemotaxis and apoptosis. *Hum Reprod Update* 2013; 19 (4): 406-18.
41. Monsivais D, Bray JD, Su E, Pavone ME, Dyson MT, Navarro A, et al. Activated glucocorticoid and eicosanoid pathways in endometriosis. *Fertil Steril* 2012; 98(1): 117-25.
42. Kyama CM, Overbergh L, Mihalyi A, Meuleman C, Mwenda JM, Mathieu C, et al. Endometrial and peritoneal expression of aromatase, cytokines, and adhesion factors in women with endometriosis. *Fertil Steril* 2008; 89(2): 301-10.
43. Hagemann T, Lawrence T, McNeish I, Charles KA, Kulbe H, Thompson RG, et al. "Re-educating" tumor-associated macrophages by targeting NF-kappaB. *J Exp Med* 2008; 205(6): 1261-8.
44. Lousse JC, Van Langendonckt A, Gonzalez-Ramos R, Defrere S, Renkin E, Donnez J. Increased activation of nuclear factor-kappa B (NF-kappaB) in isolated peritoneal macrophages of patients with endometriosis. *Fertil Steril* 2008; 90(1): 217-20.
45. Bacci M, Capobianco A, Monno A, Cottone L, Di Puppo F, Camisa B, et al. Macrophages are alternatively activated in patients with endometriosis and required for growth and vascularization of lesions in a mouse model of disease. *Am J Pathol* 2009; 175(2): 547-56.
46. Tokushige N, Markham R, Russell P, Fraser IS. Nerve fibres in peritoneal endometriosis. *Hum Reprod* 2006; 21(11): 3001-7.
47. Anaf V, Simon P, El Nakadi I, Fayt I, Buxant F, Simonart T, et al. Relationship between endometriotic foci and nerves in rectovaginal endometriotic nodules. *Hum Reprod* 2000; 15(8): 1744-50.
48. Giamberardino MA, Berkley KJ, Affaitati G, Lerza R, Centurione L, Lapenna D, et al. Influence of endometriosis on pain behaviors and muscle hyperalgesia induced by a ureteral calculosis in female rats. *Pain* 2002; 95(3): 247-57.
49. Sharpe-Timms KL. Using rats as a research model for the study of endometriosis. *Ann N Y Acad Sci* 2002; 955: 318-27.
50. Berkley KJ, Dmitrieva N, Curtis KS, Papka RE. Innervation of ectopic endometrium in a rat model of endometriosis. *Proc Natl Acad Sci U S A* 2004; 101 (30): 11094-8.
51. Berkley KJ, Rapkin AJ, Papka RE. The pains of endometriosis. *Science* 2005; 308(5728): 1587-9.
52. McAllister SL, Dmitrieva N, Berkley KJ. Sprouted innervation into uterine transplants contributes to the development of hyperalgesia in a rat model of endometriosis. *PLoS One* 2012; 7(2): e31758.
53. Chen S, Xie W, Strong JA, Jiang J, Zhang J-M. Sciatic endometriosis induces mechanical hypersensitivity, segmental nerve damage, and robust local inflammation in rats. *Eur J Pain* 2016; 20(7): 1044-57
54. Sutton CJ, Ewen SP, Whitelaw N, Haines P. Prospective, randomized, double-blind, controlled trial of laser laparoscopy in the treatment of pelvic pain associated with minimal, mild, and moderate endometriosis. *Fertil Steril* 1994; 62(4): 696-700.
55. Abbott J, Hawe J, Hunter D, Holmes M, Finn P, Garry R. Laparoscopic excision of endometriosis: a randomized, placebo-controlled trial. *Fertil Steril* 2004; 82(4): 878-84.
56. Mechsner S, Schwarz J, Thode J, Loddenkemper C, Salomon DS, Ebert AD. Growth-associated protein 43-positive sensory nerve fibers accompanied by immature vessels are located in or near peritoneal endometriotic lesions. *Fertil Steril* 2007; 88(3): 581-7.
57. Bajaj P, Bajaj P, Madsen H, Arendt-Nielsen L. Endometriosis is associated with central sensitization: a psychophysical controlled study. *J Pain* 2003; 4(7): 372-80.
58. Bove MG, Ransil BJ, Lin HC, Leem JG. Inflammation Induces Ectopic Mechanical Sensitivity in Axons of Nociceptors Innervating Deep Tissues. *J Neurophysiol* 2003;90(3):1949-55.
59. Brawn J, Morotti M, Zondervan KT, Becker CM, Vincent K. Central changes associated with chronic pelvic pain and endometriosis. *Hum Reprod Update* 2014; 20(5): 737-47
60. Li T, Mamillapalli R, Ding S, Chang H, Liu ZW, Gao XB, et al. Endometriosis alters brain electrophysiology, gene expression and increased pain sensitization, anxiety, and depression in female mice. *Biol Reprod* 2018;99(2):349-59.
61. Binkovitz LA, King BF, Ehman RL. Sciatic endometriosis: MR appearance. *J Comput Assist Tomogr* 1991; 15(3): 508-10.
62. Mirkin D, Murphy-Barron C, Iwasaki K. Actuarial analysis of private payer administrative claims data for women with endometriosis. *J Manag Care Pharm* 2007; 13(3): 262-72.
63. Torkelson SJ, Lee RA, Hildahl DB. Endometriosis of the sciatic nerve: a report of two cases and a review of the literature. *Obstet Gynecol* 1988; 71(3 Pt 2): 473-7.
64. Taylor HS, et al. Treatment of Endometriosis-Associated Pain with Elagolix, an Oral GnRH Antagonist. *N Engl J Med* 2017;377(1):28-40.
65. Guo SW. Recurrence of endometriosis and its control. *Hum Reprod Update* 2009; 15(4): 441-61.
66. Hornstein MD, Hemmings R, Yuzpe AA, Heinrichs WL. Use of nafarelin versus placebo after reductive laparoscopic surgery for endometriosis. *Fertil Steril* 1997; 68(5): 860-4.
67. Seracchioli R, Mabrouk M, Manuzzi L, Vicenzi C, Frasca C, Elmakky A, et al. Post-operative use of oral contraceptive pills for prevention of anatomical relapse or symptom-recurrence after conservative surgery for endometriosis. *Hum Reprod* 2009; 24(11): 2729-35.
68. Turner JA, Deyo RA, Loeser JD, Von Korff M, Fordyce WE. The importance of placebo effects in pain treatment and research. *JAMA* 1994; 271(20): 1609-14
69. Abbott JA, Hawe J, Clayton RD, Garry R. The effects and effectiveness of laparoscopic excision of endometriosis: a prospective study with 2-5 years follow-up. *Hum Reprod* 2003; 18(9): 1922-7.
70. Hornstein MD, Hemmings R, Yuzpe AA, Heinrichs WL. Use of nafarelin versus placebo after reductive laparoscopic surgery for endometriosis. *Fertil Steril* 1997; 68(5):860-4.
71. Culley L, Law C, Hudson N, Denny E, Mitchell H, Baumgarten M, et al. The social and psychological impact of endometriosis on women's lives: a critical narrative review. *Hum Reprod Update* 2013; 19(6): 625-39.
72. De Graaff AA, D'Hooghe TM, Dunselman GA, Dirksen CD, Hummelshoj L, Simoens S. The significant effect of endometriosis on physical, mental and social wellbeing: results from an international cross-sectional survey. *Hum Reprod* 2013; 28(10): 2677-85.
73. Fagervold B, Jenssen M, Hummelshoj L, Moen MH. Life after a diagnosis with endometriosis – a 15 years follow-up study. *Acta Obstetricia et Gynecologica* 2009; 88:914-9.
74. Fourquet J, Báez L, Figueroa M, Iriarte RI, Flores I. Quantification of impact of endometriosis symptoms on health-relate quality of life and work productivity. *Fertil Steril* 2011; 96(1):107-12.
75. Simoens S, Dunselman G, Dirksen C, Hummelshoj L, Bokor A, Brandes I, et al. The burden of endometriosis: costs and quality of life of women with endometriosis and treated in referral centres. *Hum Reprod* 2012; 27(5):1292-9.
76. Londero AP, Calcagno A, Grassi T, Marzinotto S, Orsaria M, Beltrami CA, et al. Survivin, MMP-2, MT1-MMP, and TIMP-2: their impact on survival, implantation, and proliferation of endometriotic tissues. *Virchows Arch* 2012; 461(5): 589-99.
77. Johnson NP, Hummelshoj L. Consensus on current management of endometriosis. *Hum Reprod* 2013; 28(6): 1552-68.
78. Schenken RS, Asch RH. Surgical induction of endometriosis in the rabbit: effects on fertility and concentrations of peritoneal fluid prostaglandins. *Fertil Steril* 1980; 34(6): 581-7.
79. Steinleitner A, Lambert H, Suarez M, Serpa N, Robin B, Cantor B. Periovulatory calcium channel blockade enhances reproductive performance in an animal model for endometriosis-associated subfertility. *Am J Obstet Gynecol* 1991; 164(4): 949-52.
80. Vernon MW, Wilson EA. Studies on the surgical induction of endometriosis in the rat. *Fertil Steril* 1985; 44(5): 684-94.