
PELVIC ENDOMETRIOSIS:
THE CONSEQUENCE OF UTERINE DENERVATION.

Abstract

Injuries to uterine nerves result in loss of fundocervical polarity, uterotubal dysmotility and retrograde menstruation. Ectopic endometrium, delivered by retrograde menstruation, adheres to concurrent injuries to myofascial supports and peritoneal surfaces in dependent areas of the pelvis. Varying laparoscopic appearances depend on the site, nature, extent, and timing of tissue injury as well as the concurrent availability of endometrium. Asymmetry of uterosacral ligaments with little, or no, ectopic endometrium (stage 0-1, revised AFS) often follows intrapartum injuries, whereas symmetrical hypertrophy of the uterosacral ligaments with large volumes of ectopic endometrium (stage 3-4, revised AFS) often follows prolonged straining during defecation that is common in nulliparous presentations of endometriosis. Tissue repair that includes aberrant reinnervation in the uterine isthmus, cervix, vagina and uterosacral ligaments, contributes to classical symptoms of chronic pelvic pain, dysmenorrhea, dyspareunia and subfertility some time after the primary injuries.

Key words:

Endometriosis, Chronic pelvic pain, Denervation, Reinnervation.

Clinical presentations of endometriosis are often disproportionate to findings at laparoscopy. These, and other paradoxical observations, raise the recurrent question as to whether endometriosis is a cause or consequence of chronic pelvic pain.¹ This account takes the view that pelvic deposits of endometrium are largely a consequence of prior injuries to pelvic autonomic nerves, myofascial supports and peritoneal surfaces.²

Injuries to pelvic autonomic nerves result from difficult vaginal delivery, straining during defecation, and trauma including surgery (Fig. 1).³ The first response of injured autonomic nerves is to become metabolically active and re-grow in a chaotic fashion from the proximal stump to attempt to restore lost functions.⁴ Aberrant reinnervation leads to progressive increases in nerve fiber density and eventually, over several years, to “pain or discomfort in response to light touch” (allodynia). Injuries to uterine nerves also cause retrograde menstruation, loss of fundocervical polarity and uterotubal dysmotility.^{5,6} Ectopic endometrium, if it is available at the time of the injury, attaches to injured myofascial supports and peritoneal surfaces. Painful clinical symptoms, including chronic pelvic pain, dysmenorrhea, dyspareunia and subfertility, result from subsequent, aberrant reinnervation of the uterine isthmus, cervix, upper vagina, uterosacral ligaments, peritoneal surfaces and deposits of endometrium.²

Evidence to support each step in this argument has become available in recent years and asserts the significance of underlying injuries to pelvic nerves over the effects of deposits of ectopic endometrium. Clinical research confirms that surgical destruction of ectopic endometrium carries little clinical benefit, and, patients with chronic pelvic pain with, or without, endometriosis improve with GnRH analogues and demonstrate similar, high densities of abnormal reinnervation.⁷⁻⁹ By necessity this account cannot deal with every facet of endometriosis but it does set out a clinical framework of pelvic autonomic denervation and reinnervation whose consequences may contribute to many different gynecologic presentations.¹⁰

Contemporary theories of endometriosis and chronic pelvic pain

Dr John Sampson (Albany, NY) proposed retrograde menstruation as the mechanism for pelvic endometriosis.¹¹⁻¹⁴ Coelomic metaplasia, lymphovascular metastasis and immunogenetic theories, have not displaced Sampson's original observations. There has, however, been no satisfactory explanation of retrograde menstruation, nor the different laparoscopic appearances of pelvic endometriosis, and, the sources of different clinical symptoms. Empiric, clinical observations have not clarified the cause of endometriosis with, or without, chronic pelvic pain; indeed, they continue to create complexity and confusion. The original observations of Dr Howard Taylor¹⁵⁻¹⁷ (New York, NY), Drs Willard Allen and Howard Masters¹⁸⁻¹⁹ (St Louis, MO), Dr KE Krantz²⁰ (New York, NY) in the 1950's, and, Dr AC Richardson²¹⁻²² in more recent times, provide the basis for much of the present view and merit re-examination in this new framework.

In an address to the Tuskegee Medical Society in 1957, Dr HC Taylor¹⁷ said, with considerable insight, that;

“two processes seem to be operative in the production of these symptoms (pelvic pain), namely a hyperalgesia or hypersensitivity of the tissues and a vascular disorder in the form of a hyperaemia or pelvic congestion.”

Also, in the pre-laparoscopy era, Drs Allen and Masters drew attention to clinical presentations of chronic pelvic pain with myofascial “defects” after difficult labors, that resulted in a “universal joint cervix”, and, additional myofascial defects at laparotomy (Allen-Masters syndrome).¹⁸ Besides the original form of vaginal “defects” it is now clear that the consequences of vaginal delivery include levator, uterosacral and neurologic defects.² Allen and Masters originally attempted primary, surgical repair of fascial and peritoneal defects at laparotomy¹⁸ though this later gave way to hysterectomy in the treatment of these clinical presentations of chronic pelvic pain.¹⁹ In this second paper, Dr Allen took the view that premature

maternal voluntary efforts and minor malpresentations in labour may be sources of significant maternal injury.

In more recent times, Dr AC Richardson (Atlanta, GA) defined the primary axis of pelvic support as the line of the uterosacral ligaments, rectovaginal septum and perineal body, underpinned by the levator ani.^{21,22} Unilateral, or bilateral, vaginal defects contribute to uterovaginal prolapse and urinary stress incontinence.²² Injuries to the levator ani (“levator defects”) also contribute to loss of uterovaginal support, and, frequently occur in women with chronic pelvic pain (Fig. 2).²³ Avulsion, attenuation and asymmetry of uterosacral and cardinal ligaments (“uterosacral defects”) have received less attention though concomitant injuries to their central neurovascular bundles and subsequent, aberrant reinnervation may contribute to some patterns of chronic pelvic pain (Fig. 3-4).² Laparoscopic evaluation of chronic pelvic pain traditionally relies on demonstrating the presence of adhesions, endometriosis or signs of infection. In many cases the cause for pain is not immediately apparent though few clinicians ascribe significance to these (sometimes subtle) uterosacral injuries (Fig. 3e & 3f), nor the disruption of their insertions into the rectovaginal septum in cases of “deep infiltrating endometriosis”.²

In 1841, Dr Robert Lee (London, UK) described the pelvic autonomic nerves in fresh, postpartum cadavers preserved in alcohol (Fig 1).²⁴ His series of careful dissections and detailed illustrations, confirmed in other species, are an important landmark in the specialty. Many, post-1945 medical schools preserved cadaveric material in formalin that destroys fine branches of autonomic nerves with the consequence that several generations of medical graduates have been unfamiliar with their precise anatomic detail.²⁵ Nerve trunks from the inferior hypogastric plexus converge on the uterovaginal plexus at the vaginal vault before accompanying the uterine artery to the uterine isthmus. Proximal branches of the inferior hypogastric plexus deliver important uterine nerves along the central neurovascular bundle of the uterosacral

ligaments.²⁶ Dr KE Krantz (Kansas City, KS) described the original features of intrinsic uterine innervation by identifying important nerve plexi in the subserosal layers, and, at the endometrial-myometrial interface (Fig 4a).²⁰ Aberrant reinnervation in structures at, and around, the junction of the uterus and vagina, have been described by a number of groups in recent years in women with chronic pelvic pain with, or without, endometriosis (Fig 4b-e).²⁷⁻³⁵ Affected structures include the isthmus of the uterus, uterine cervix, upper vagina, uterosacral ligaments, retroperitoneum and deposits of ectopic endometrium.

Causes of pelvic denervation

In 1957 Professor Sir Dugald Baird expressed his view about the relationship between intrapartum events and subsequent gynecologic presentations:³⁶

“the great majority of ailments encountered in gynaecological practice are the result of infections and injuries contracted during parturition.”

Relationships between difficult intrapartum episodes and subsequent injuries to the levator ani with prolonged, pudendal nerve terminal latencies have been clearly established in prospective studies over five years.³⁷ Recent magnetic resonance imaging in women with chronic pelvic pain describe different degrees of “levator defects” depending on avulsion (a) from its pubic origins, (b) from its muscular origins over obturator internus, and, (c) from its somatic nerve supply (Fig. 2a-d).²³ Women with chronic pelvic pain frequently demonstrate partial or complete avulsion of the levator ani from its muscular origin over obturator internus.²³

The pelvic autonomic nerve trunks lie medial to the levator ani. Any injury to the levator ani may occur with concurrent injuries to these pelvic autonomic nerve trunks. Asymmetric patterns of reinnervation in the uterine isthmus and cervix, including collateral sprouting of nerve bundles, are pathognomonic for a

traumatic etiology and are frequent following hysterectomy for chronic pelvic pain with, or without, endometriosis (Fig. 4c).²⁸ Preliminary results of prospective longitudinal studies of 2240 nulliparous women over four years from a birth cohort delivered in 1992 confirm relationships between difficult intrapartum episodes and subsequent, painful, gynecologic symptoms.³⁸ “Difficult” intrapartum episodes included those associated with induction of labor, prolonged labor (an active phase lasting more than twelve hours), prolonged maternal efforts in the second stage of labor (greater than two hours), operative vaginal delivery, malpresentations, and, fetal weight greater than 4000 grams.

Other important causes of uterine denervation include straining during defecation.³⁵ Straining during defecation is epidemic in Western societies.³⁹ Three per thousand adults have stool frequencies of less than one per month, one per cent less than once per week with physical efforts complicating 20-30% of Western bowel movements. There are few studies of persistent straining during defecation owing to the ambiguity of the term “constipation” that has different and varied meanings in different studies.⁴⁰ It may mean hard, small or infrequent stools that are difficult to deliver. Persistent straining during defecation, or, in the second stage of labor, cause specific neuro-immunohistochemical lesions across the pelvis from the uterus to the vulva.³⁵ Widespread, perivascular nerve fiber proliferation (PVNFP) presents with premenstrual pain from affected sites along the lower genital tract (Fig 4d). In nulliparous women, chronic pelvic pain, with advanced endometriosis, frequently results from straining during defecation that results in perivascular nerve fiber proliferation in the uterus.^{28,35} Painful symptoms may originate at different anatomic sites in the bladder, vulva, vagina or uterus, through increased blood flow and vasodilatation through allodynic or hyperalgesic mechanisms as the distension of blood vessels applies direct mechanical stimuli to layers of abnormal nerves (Fig. 4d). These observations provide biological explanations for Dr HC Taylor’s prescient observations over fifty years ago (Fig. 4d).¹⁵⁻¹⁷

Consequences of pelvic denervation

Physiological studies of autonomic denervation emphasise the development of “supersensitivity” following injury to an autonomic nerve with accompanying changes in the central nervous system (“central sensitisation”).⁴¹ Aberrant reinnervation in a different pelvic organs results in chronic pelvic pain, dyspareunia, irritative bladder and irritable bowel symptoms.^{27-34, 42-44} Epidemiological studies of women with chronic pelvic pain with, or without endometriosis, confirm high rates of coexistent painful or irritative symptoms in anatomically-adjacent organs.⁴⁵⁻⁴⁶ Recurrent pain occurs within five years in 10-50% of patients following hysterectomy for chronic pelvic pain owing to “sensitisation” of the central nervous system.⁴⁷⁻⁴⁸

Injuries to autonomic nerves may also cause loss of visceral function, tissue hypoplasia or hyperplasia, visceral dysmotility, and, susceptibility to infection, stress, tobacco, and, alcohol (Table 1). Each has clinical associations with endometriosis. Dynamic ultrasound and magnetic resonance imaging show evidence of dyspolar uterine activity, including hyperperistalsis and dysperistalsis, in both nulliparous and multiparous women with endometriosis and adenomyosis.^{5,6} Pre-pregnancy neural injuries may contribute to suboptimal reproductive outcomes including preeclampsia, preterm labour and antepartum hemorrhage may relate to these injuries.⁵³ Pelvic endometriosis frequently coexists with different forms of uterine hyperplasia in adenomyosis and leiomyomas.⁵⁶ Recent studies confirm loss of nerves at the endometrial-myometrial interface in some forms of adenomyosis, and, loss of nerves in the myometrium in many leiomyomas (Fig 4f).⁴⁹⁻⁵² Denervation of epithelial surfaces changes the spectrum of susceptibility to infection from Gram positive organisms to Gram negative and opportunist organisms⁵⁴ and may contribute to increased rates of vulvovaginal infection in endometriosis.⁵⁵

Different laparoscopic appearances result from the site, nature, frequency and extent of the tissue injury together with the concurrent availability of endometrium (Fig. 3a-f).² For example, in young, nulliparous women, recurrent injuries caused by daily straining during defecation, result in symmetric, hypertrophic uterosacral ligaments with fusion of rectum to vagina, and in some cases, large volumes of endometriosis adhering to injured peritoneal surfaces (revised AFS Stage 3-4).² Sporadic injury following difficult vaginal delivery results in retrograde menstruation in association with avulsion or attenuation of myofascial supports. Retrograde menstruation may be limited, or absent, if breast-feeding or contraception prevents menstruation during repair of the intrapartum injury leading to little, or no, ectopic endometrium at laparoscopy (revised AFS, Stage 0-1). Other laparoscopic phenotypes, including “deep infiltrating endometriosis”, may result from a number of circumstances (Table 2). Injuries to the cervix, vagina and abdominal wall may contribute to deposition of ectopic endometrium in cases of cervical endometriosis, endometriosis in episiotomy and Cesarean section scars. For each clinical phenotype, it is often possible to identify a clear history of tissue injury and repair involving processes affecting pelvic nerves and myofascial supports.

Chronic pelvic pain, without endometriosis, demonstrates similar treatment responses with GnRH agonists⁶, and, similar neuro-immunohistochemical findings⁷ to matched groups of patients with endometriosis. These studies find no apparent differences between women with chronic pelvic pain with, or without, endometriosis suggesting that endometriosis plays a limited role in many clinical presentations. Aberrant reinnervation of deposits of ectopic endometrium occurs to some degree though the density of reinnervation is minor compared to adjacent reinnervation in the uterine isthmus, uterine cervix, vagina and uterosacral ligaments.³³ Pain during, and after, menstruation may result from peritoneal irritation by menstrual loss, and, amplified by aberrant reinnervation of peritoneal surfaces and endometrial deposits.

Conclusion

Anatomic consequences of vaginal delivery include vaginal, levator, uterosacral and neurologic defects.

Drs W Allen and WH Masters described many of the macroscopic injuries in 1955; Dr HC Taylor inferred the neurologic injuries on clinical grounds alone in 1954. In contemporary clinical practice the laparoscopic appearances of the anatomic injuries associated with vaginal delivery are the opposite of those associated with, often nulliparous, efforts of straining during defecation. This dichotomy has caused considerable confusion. The physiologic consequences of autonomic denervation are diverse, cumulative, and, include changes in visceral form and function, susceptibility to infection and toxins, as well as aberrant reinnervation and its consequences in the central nervous system. Pelvic endometriosis and its clinical associations are simply developments of the anatomic and physiologic consequences of vaginal delivery, straining during defecation, and, other as yet unidentified, sources of injury to pelvic autonomic nerves. Developing this framework may avert some of the aetiological confusion and therapeutic difficulty in contemporary clinical presentations of endometriosis, and, contribute to an understanding of other clinical, gynaecological presentations.

Acknowledgements

This paper owes a great deal to conversations with the late Drs A. Cullen Richardson and Kermit E. Krantz before their respective passings. The author also thanks many colleagues at the University of North Carolina at Chapel Hill and Duke University who have contributed to the development of these ideas.

References

- (1) Slocumb JC.
Chronic somatic, myofascial, and neurogenic abdominal pelvic pain.
Clin Obstet Gynecol. 1990; 33(1): 145-53.
- (2) Quinn M.
Endometriosis: an elusive epiphenomenon. J Obstet Gynaecol 2009; 29(7):590-3.
- (3) Stoll G, Muller HW.
Nerve injury, axonal regeneration and neuronal regeneration: basic insights.
Brain Pathol 1999; 9(2): 313-25.
- (4) Cervero F.
Visceral hyperalgesia - revisited. Lancet 2000; 356:1127-8.
- (5) Kissler S, Hamscho N, Zangos S, Wiegratz I, Schlichter S, Menzel et al
Uterotubal transport disorder in adenomyosis and endometriosis—a cause for infertility.
Brit J Obstet Gynaecol. 2006; 113(8):902-8.
- (6) Leyendecker G, Kunz G, Wildt L, Beil D, Deininger H.
Uterine hyperperistalsis and dysperistalsis as dysfunctions of the mechanism of rapid sperm transport in patients with endometriosis and infertility.
Hum Reprod. 1996; 11(7): 1542-51.
- (7) Sutton CJG, Ewen SP, Whitelaw N, Haines P.
Prospective, randomised, double blind, controlled trial of laser laparoscopy in the treatment of chronic pelvic pain associated with minimal, mild and moderate endometriosis.
Fertil Steril 1992; 62(4):696-700.

- (8) Ling FW.
Randomised controlled trial of depot leuprolide in patients with chronic pelvic pain and clinically suspected endometriosis. *Obstet Gynecol* 1999; 93:51-8.
- (9) Atwal GSS, Duplessis D, Armstrong GR, Slade RJ, Quinn MJ.
Uterine innervation after hysterectomy for chronic pelvic pain with, or without, endometriosis. *Am J Obstet Gynecol* 2005; 193:1658-1663.
- (10) Quinn M, Slack MC, Kirk N, Harris MD.
Obstetric denervation-gynecologic reinnervation. *Am J Obstet Gynecol* 2002; 186(1): 168.
- (11) Sampson JA.
Perforating hemorrhagic (chocolate) cysts of the ovary. Their importance and specially their relation to pelvic adenomas of endometriotic type ("adenomyoma" of the uterus, rectovaginal septum, sigmoid etc.) *Arch Surg* 1921; 3: 245–322.
- (12) Sampson JA.
Benign and malignant endometrial implants in the peritoneal cavity and their relation to certain ovarian tumors. *Surg Gynecol Obstet* 1924; 38: 287–311.
- (13) Sampson JA.
Endometrial carcinoma of the ovary arising in endometrial tissue in that organ. *Arch Surg* 1924; 10: 1–72.
- (14) Sampson JA.
Peritoneal endometriosis due to the menstrual dissemination of endometrial tissue into the peritoneal cavity. *Am J Obstet Gynecol* 1927; 14: 422–46.

- (15) Taylor HC.
Vascular congestion and hyperemia; their effect on function and structure in the female reproductive organs; etiology and therapy. *Am J Obstet Gynecol.* 1949; 57(4): 654-68.
- (16) Taylor HC.
Pelvic pain based on a vascular and autonomic nervous system disorder.
Am J Obstet Gynecol. 1954; 67(6): 1177-96.
- (17) Taylor HC.
The Clinical Management of Functional Pelvic Pain. *J Nat Med Ass* 1957, 49;6:368-70.
- (18) Allen WM, Masters WH.
Traumatic laceration of uterine support. *Am J Obstet Gynecol* 1955; 70:500-513.
- (19) Allen WM.
Chronic pelvic congestion and pelvic pain. *Am J Obstet Gynecol* 1971; 109:198-202.
- (20) Krantz, KE.
Innervation of the human uterus. *Ann N Y Acad Sci.* 1959; 75:770-84.
- (21) Richardson AC.
The rectovaginal septum revisited: its relationship to rectocele and its importance in rectocele repair. *Clin Obstet Gynecol.* 1993; 36(4): 976-83.
- (22) Richardson AC.
Female pelvic floor support defects. *Int Urogynecol J Pelvic Floor Dys* 1996;7(5): 241.
- (23) Quinn M.
Levator defects and chronic pelvic pain. *J Obstet Gynaecol* 2007; 57(3):357-62.
- (24) Lee R.
On the nervous ganglia of the uterus, and an appendix to a paper on the nervous ganglia of the

uterus, with a further account of the nervous structures of that organ.

Phil Trans 1841 i 269-75.

- (25) Spackman R, Wrigley B, Roberts A, Quinn M.
The inferior hypogastric plexus: a different view. *J Obstet Gynaecol.* 2007; 27(2):130-3.
- (26) Campbell RM.
The anatomy and histology of the sacrouterine ligaments. *Am J Obstet Gynecol* 1950; 59:1-12.
- (27) Quinn MJ, Kirk N.
Uterine innervation following hysterectomy for chronic pelvic pain.
Am J Obstet Gynecol 2002; 187:1515-1520.
- (28) Tokushige N, Markham R, Russell P, Fraser IS.
High density of small nerve fibres in the functional layer of the endometrium in women with endometriosis. *Hum Reprod.* 2006; 21(3):782-7.
- (29) Tokushige N, Markham R, Russell P, Fraser IS.
Different types of small nerve fibers in eutopic endometrium and myometrium in women with endometriosis. *Fertil Steril.* 2007; 88(4):795-803.
- (30) Al-Jefout M, Andreadis N, Tokushige N, Markham R, Fraser IS.
A pilot study to evaluate the relative efficacy of endometrial biopsy and full curettage in making a diagnosis of endometriosis by the detection of endometrial nerve fibers.
Am J Obstet Gynecol. 2007; 197: 578.
- (31) Zhang XM, Lu B, Huang X, Xu H, Zhou C, Lin J.
Endometrial nerve fibers in women with endometriosis, adenomyosis, and uterine fibroids.
Fertil Steril. 2009; 92:1799-1801.

- (32) Zhang XM, Yao HJ, Huang XF, Lu BC, Xu H, Zhou CY.
Nerve fibres in ovarian endometriotic lesions in women with ovarian endometriosis.
Hum Reprod 2010; 25(2):392-7.
- (33) Kelm Junior AR, Lancellotti CL, Donadio N, Auge AP, Lima SM, Aoki T, Ribeiro PA.
Nerve fibers in uterosacral ligaments of women with deep infiltrating endometriosis.
J Reprod Immunol. 2008; 79(1):93-9.
- (34) Quinn M, Kirk N.
Uterosacral nerve fibre proliferation in parous endometriosis.
J Obstet Gynaecol. 2004;24(2):189-90.
- (35) Quinn M.
Perivascular nerve fiber proliferation; the consequence of prolonged straining.
J Obstet Gynaecol 2007; 27(2):185-8.
- (36) Professor Sir Dugald Baird. Preface to the 6th edition, "Combined Textbook of Obstetrics and Gynaecology", Livingstone, 1957.
- (37) Snooks SJ, Swash M, Mathers SE, Henry MM.
Effect of vaginal delivery on the pelvic floor: a 5-year follow-up.
Br J Surg. 1990; 77(12):1358-60.
- (38) Golding J.
Measuring outcomes in a longitudinal birth cohort.
Paediatr Perinat Epidemiol. 2009; 23 Suppl 1:185-200.
- (39) Heaton KW, Cripps HA.
Straining at stool and laxative taking in an English population. Dig Dis Sci 1993; 38:1004-8.
- (40) Probert CS, Emmett PM, Cripps HA, Heaton KW.
Evidence for the ambiguity of the term constipation: the role of irritable bowel syndrome.

Gut. 1994; 35(10):1455-8.

- (41) Janig W.

Integrative action of the autonomic nervous system: neurobiology of homeostasis.

Cambridge University Press, 2006.

- (42) Westrom LV, Willen R.

Vestibular nerve fiber proliferation in vulvar vestibulitis syndrome.

Obstet Gynecol 1998; 91:572-6.

- (43) Schofield EC, Clausen JA, Burcher E, Moore KH.

GAP- Immunoreactivity of subepithelial and detrusor muscle nerve fibres in patients with refractory idiopathic detrusor overactivity. *Neurourol Urodynam* 2005; 24:325-33.

- (44) Chan CLH, Facer P, Davis JB, Smith GD, Egerton J, Bountra C, Williams NS, Anand P.

Sensory fibre expressing capsaicin receptor TRPV-1 in patients with rectal hypersensitivity and faecal urgency. *Lancet* 2003; 361: 385-91.

- (45) Zondervan KT, Yudkin PL, Vessey MP, Dawes MG, Barlow DH, Kennedy SH.

Prevalence and incidence of chronic pelvic pain in primary care: evidence from a national general practice database. *Brit J Obstet Gynaecol* 1999; 106:1149-55.

- (46) Zondervan KT, Yudkin PL, Vessey MP, Dawes MG, Barlow DH, Kennedy SH.

Patterns of diagnosis and referral in women consulting for chronic pelvic pain in UK primary care. *Brit J Obstet Gynaecol* 1999; 106:1156-61.

- (47) Namnoum AB, Hickman TN, Goodman SB.

Incidence of symptom recurrence after hysterectomy for endometriosis.

Fertil Steril. 1995; 64: 898-902.

- (48) MacDonald SR, Klock SC, Milad MP.
Long-term outcome of nonconservative surgery (hysterectomy) for endometriosis-associated pain in women <30 years old. *Am J Obstet Gynecol.* 1999;180(6):1360-3.
- (49) Quinn M.
Uterine innervation in adenomyosis. *J Obstet Gynaecol* 2007;27(3):287-91.
- (50) Quinn M.
Uterine innervation in fibroids. *J Obstet Gynecol* 2007; 27(5):489-92.
- (51) Savitskiĭ GA, Morozov VV, Svechnikova FA, Ivanova RD.
Pathogenesis of uterine myoma. *Akush Ginekol (Mosk).* 1981;(4):13-5.
- (52) Savitskiĭ GA, Skopichev VG, Rakitskaia VV.
"Denervation" of the tumor node as one of the elements of the pathogenesis of uterine myoma.
Akush Ginekol (Mosk). 1986; (2):24-7.
- (53) Stephansson O, Kieler H, Granath F, Falconer H.
Endometriosis, assisted reproduction technology, and risk of adverse pregnancy outcome.
Hum Reprod. 2009 24(9):2341-7.
- (54) Straub RH.
Autoimmune disease and innervation. *Brain Behav Immun.* 2007; 21(5):528-34.
- (55) Gemmill JA, Stratton P, Cleary SD, Ballweg ML, Sinaii N.
Cancers, infections, and endocrine diseases in women with endometriosis.
Fertil Steril. 2010; 94(5): 1627-31.
- (56) Huang JQ, Bunker Lathi R, Lemyre M, Rodriguez HE, Nezhat CH, Nezhat C.
Coexistence of endometriosis in women with symptomatic leiomyomas.
Fertil Steril. 2010; 94(2):720-3.

Legends

Figure 1

The uterine nerves. The nerve supply of the pelvic viscera in a fresh prosection preserved in methanol, rather than formalin, demonstrating (a) the superior hypogastric plexus, (b) the hypogastric nerve, (c) the inferior hypogastric plexus, (d) the uterovaginal plexus, (e) parasympathetic fibres from sacral segments (S2-4).

Mixed autonomic nerves converge on Frankenhauser's uterovaginal nerve plexus at the vaginal vault where they are vulnerable to intrapartum injury or persistent, straining during defaecation.

Prosection by Dr Ross Spackman and Dr Alice Roberts, following preparation by Bill Wrigley, University Department of Anatomy, Bristol.

Figure 2

Levator injuries (or "defects", LAd) in chronic pelvic pain.

(a) Axial section of proximal urethra in normal nulliparous subject. The levator ani is symmetrical and intact.

(b) Unilateral, right-sided avulsion from pubic origin (LAd 1). Clinical examination reveals a tender bulge on the posterior vaginal wall.

(c) Bilateral, avulsions from the fascial origin from obturator internus (LAd 2). This is the most frequent injury in women with chronic pelvic pain associated with over 70% of clinical presentations. Physical findings include tenderness over the muscular origins)

(d) Denervation of levator ani with bilateral avulsions from the pubis and obturator origins (LAd 3). Complete loss of form and function of the levator ani, can be detected on physical examination and confirmed by electrophysiological studies.

Figure 3

Uterosacral injuries (or “defects”). Unilateral or bilateral, asymmetry, attenuation and avulsion of uterosacral ligaments are common in women with chronic pelvic pain.

- (a) Normal uterosacral arch in an asymptomatic nulliparous woman.
- (b) Avulsion of the right uterosacral ligament in a woman with chronic pelvic pain.
- (c) Avulsion of the left uterosacral ligament that has been replaced by varices along its course.
- (d) Avulsion of the left uterosacral ligament and attenuation of the right uterosacral ligament in a woman with chronic pelvic pain.
- (e) Symmetrical attenuation of the uterosacral ligaments following hyperstimulation of the uterus associated with induction of labor with prostaglandin pessaries
- (f) Typical injury to the left uterosacral ligament where there is loss of the uterosacral arch and asymmetry of the ligaments.

Figure 4

Neurologic injuries (or “defects”). Different patterns of uterine denervation and reinnervation following hysterectomy for chronic pelvic pain with, or without endometriosis (x 200).

- (a) normal myometrium, (x 100)
- (b) aberrant reinnervation in myometrial stroma,
- (c) collateral sprouting of nerve bundles following intrapartum injury,
- (d) perivascular nerve fibre proliferation around small blood vessels,
- (e) aberrant reinnervation in the uterosacral ligaments
- (f) loss of nerves in leiomyoma

(1) Loss of visceral form (hypoplasia or hyperplasia)

In an organ capable of physical enlargement such as the uterus, denervation manifests as localised hyperplasia in the forms of adenomyosis⁴⁹ or leiomyoma.⁵⁰⁻⁵²

(2) Loss of visceral function

Injury to uterine nerves results in uterotubal dysmotility and retrograde menstruation.^{5,6} These processes may also contribute to adverse pregnancy outcomes including preeclampsia and intra-uterine growth retardation.⁵³

(3) Increased susceptibility to infection

Injury to uterine and vaginal nerves may contribute to different patterns of opportunist⁵⁴ and vulvovaginal infections⁵⁵.

(4) Increased susceptibility to other irritants

Injuries to autonomic nerves are susceptible to alcohol, tobacco, cocaine, drugs, pharmacological agents, etc resulting in changes in the onset or course of different clinical conditions both within, and beyond, the female pelvis.

(5) Pain associated with local, aberrant reinnervation

Injury to uterine nerves result in different patterns of aberrant reinnervation and chronic pelvic pain, menstrual disturbances, dysmenorrhea and dyspareunia.^{27-34, 42-44}

(6) Pain associated with central “sensitisation”

Hysterectomy and bilateral salpingo-oophorectomy combined with removal of “endometriosis” does not necessarily remove the symptoms of pain. Central “sensitisation” results in persistent or recurrent symptoms in many women with advanced “endometriosis”.^{47, 48}

Table 1

Consequences of pelvic autonomic denervation. Injuries to pelvic autonomic nerves may contribute to different, adverse obstetric and gynecologic outcomes. These principles may also apply to injuries to branches of the cardiac and celiac plexi in the thorax and abdomen respectively.⁵⁵

Tissue injury	Subsequent laparoscopic phenotype following tissue repair
Ovulation with injury to the surface of the ovary.	Painless endometriotic cyst (“endometrioma”)
Persistent physical efforts during defecation (often in young, nulliparous women).	Symmetrical, hypertrophy of uterosacral ligaments with large volumes of associated endometriosis.
Prior difficult, intrapartum episode some years earlier e.g. prolonged labor, prolonged second stage of labor, malpresentations, forceps, etc.	Asymmetry of uterosacral ligaments with some degree of peritoneal neovascularisation, with or without, endometriosis.
History of a prior difficult, intrapartum episode some years earlier e.g. during second stage of labor, forceps delivery	Disruption of the insertions of the uterosacral ligaments as they insert into the rectovaginal septum. (“deep infiltrating endometriosis”)
Sharp curettage associated with excessive traction on the cervix	Enlarged uterus associated with adenomyosis and small volumes of endometriosis at the insertion of the uterosacral ligaments with, or without, adhesions.
Bladder, ureteric, bowel, cervix and vaginal endometriosis.	Intrapartum injury to the respective organ or concurrent, full thickness pathology including the serosal surface of the organ e.g. Crohn’s disease.

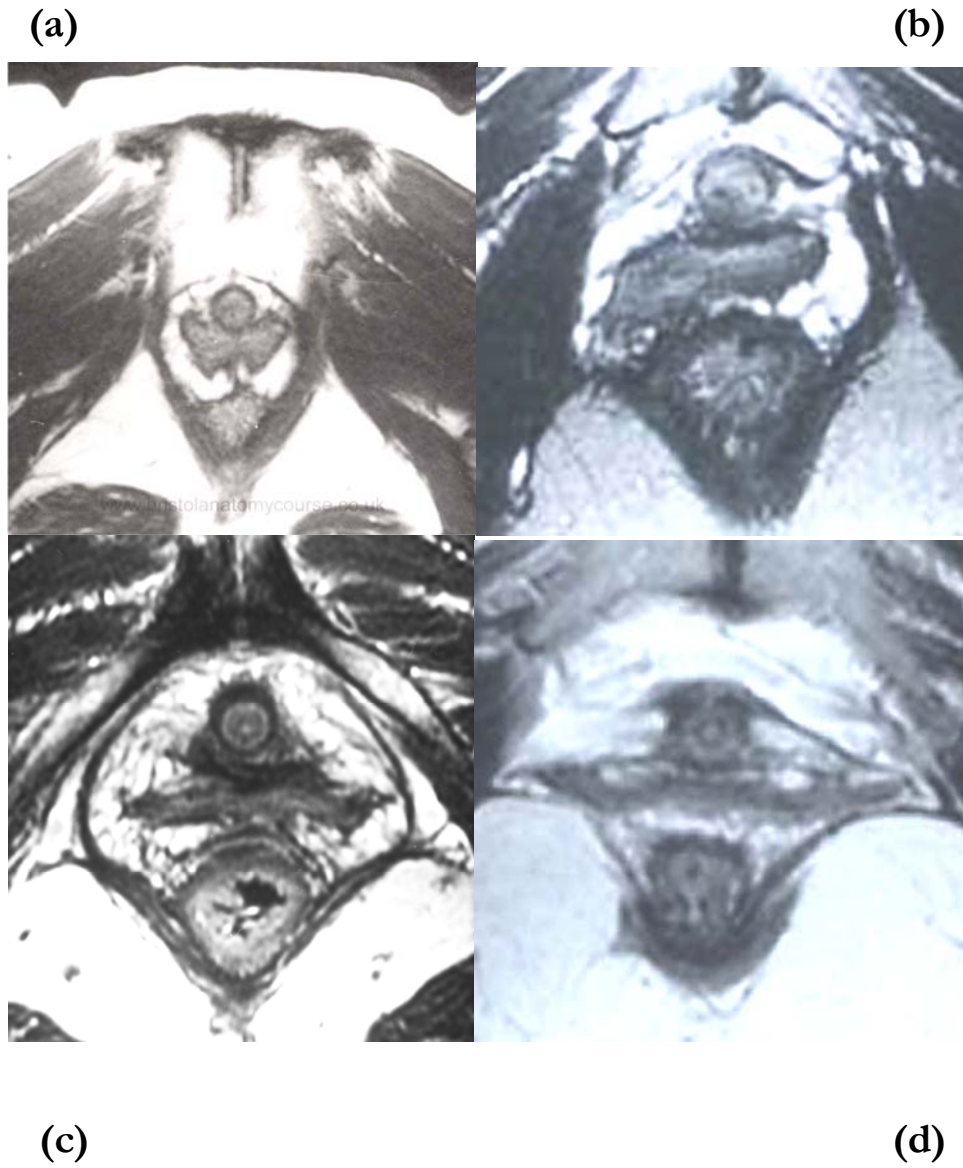
Table 2

Mechanisms of tissue injury and repair that contribute to different, laparoscopic appearances associated with chronic pelvic pain with, or without, endometriosis.

Figure 1



Figure 2 Levator defects in chronic pelvic pain.



Levator “defects” (LAd) in chronic pelvic pain.

Figure 3 Uterosacral defects in chronic pelvic pain

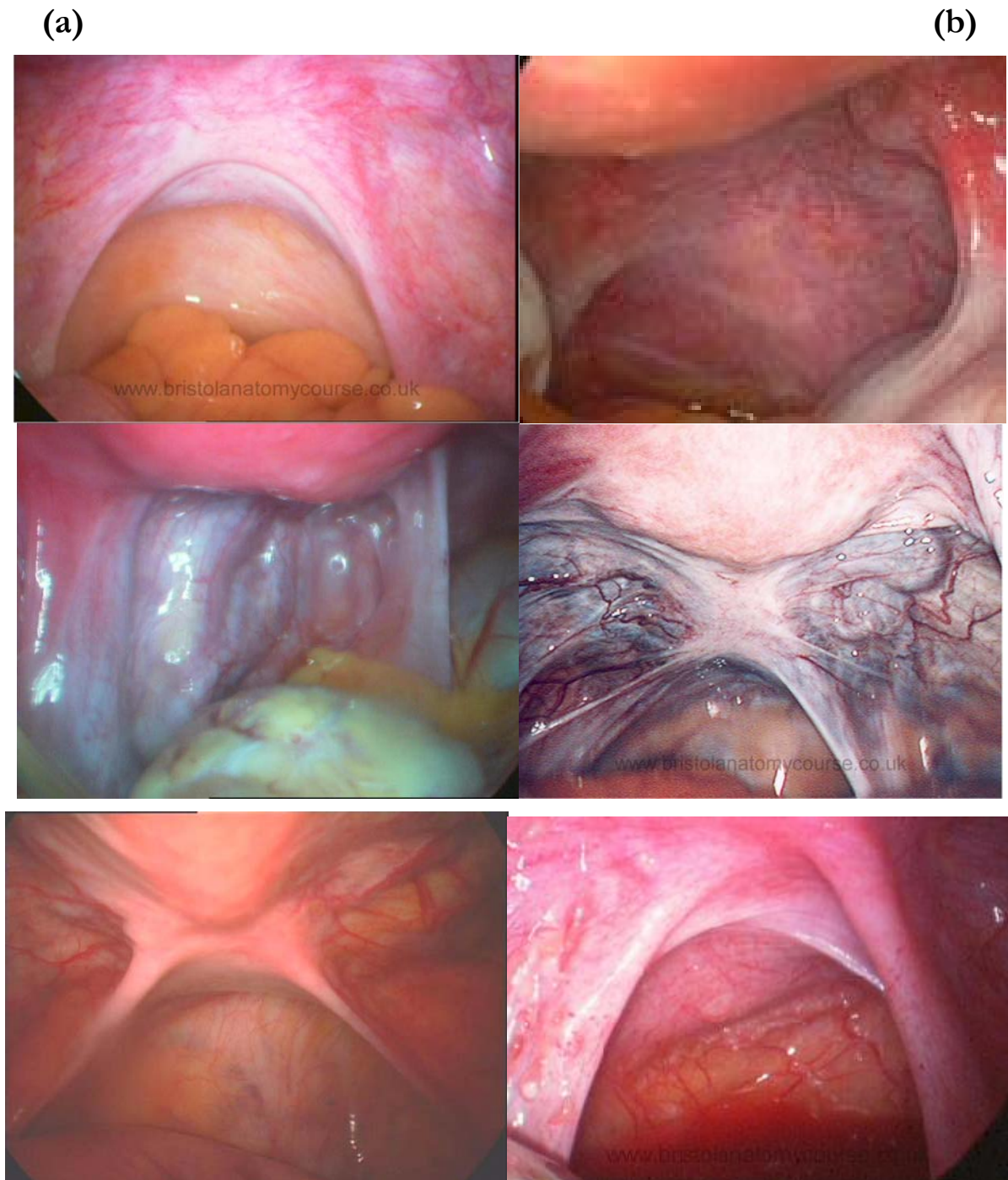


Figure 4 Neurologic defects with ensuing patterns of tissue repair in women following hysterectomy for chronic pelvic pain and endometriosis.

