
**ENDOMETRIOSIS:
THE ELUSIVE EPIPHENOMENON.**

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Endometriosis is characterised by “aetiological confusion and therapeutic anarchy” (Garry, 2004). Over the past century many theories have emerged though without an explanation, and the means for prevention, gynaecology cannot be said to have come of age. This account provides a new view of endometriosis based on pelvic denervation causing retrograde menstruation with ectopic endometrium adhering to injured tissues. Protection of pelvic nerves makes prevention possible.

Explaining the enigma depends on explaining some of its paradoxes. Many women have pain before the finding of endometriosis; others develop similar pain after complete removal of their pelvic organs. Young, nulliparous women often present with advanced endometriosis (AFS grade III/IV) whereas women in their middle years, with similar symptoms, present with minor deposits (AFS grade I/II). Young nulliparous women also have hypertrophic myofascial supports with fusion of their vagina and rectum whereas multiparous women have injured and atrophic ligaments. Treatment has variable results with prompt recurrence of pain following radical surgery in some circumstances, and, amelioration of pain by GnRH agonists in others. What is the specific evidence that endometriosis causes pain – there are many theories, few answers. These observations prompted the view that endometriosis is a manifestation rather than a cause of chronic pelvic pain (Slocumb, 1992).

The denervation-reinnervation view

Branches of the inferior hypogastric plexi converge on the uterovaginal plexus at the vaginal vault where they are vulnerable to injury. Recent studies confirm abnormal nerves in the myometrium, endometrium, cervix, uterosacral ligaments and retroperitoneum in women with chronic pelvic pain with, or without, endometriosis (Atwal, 2005; Tokushige, 2006, 2007). Improving laparoscopic techniques describe frequent, extensive, postpartum injuries to the uterosacral ligaments (Fig 1b-c). The relationship between difficult intrapartum episodes, myofascial injuries and subsequent pelvic pain was described in the 1950's (Allen, 1955). Interpreting these wide-ranging injuries to muscles, ligaments, nerves and blood vessels in women with chronic pelvic pain, remains empirical rather than based on specific sequences of events in an individual woman's clinical history

In a nulliparous woman with extensive endometriosis there is often a clear history of straining to achieve defaecation; in multiparous women there is usually a prior, difficult intrapartum episode. In both circumstances there are injuries to myometrial nerve fibres and neural regeneration in characteristic patterns (Fig. 2b, Atwal, 2005). The typical, nulliparous, neurological lesion describes injured nerves regrowing along small blood vessels (perivascular nerve fibre proliferation, PVNFP, Fig 2d). In the multiparous woman, collateral sprouting of nerve fibres

suggests a traumatic injury with tearing of nerve bundles, collateral sprouting and widespread stromal reinnervation (2b-2c)

If different patterns of neural injury are the primary source of the cardinal clinical symptoms of dysmenorrhea, dyspareunia, menstrual problems and subfertility, then in the denervation-reinnervation view the prior sequence of events is set out in Table 1.

- 1) Injury to uterine nerves through prolonged straining to achieve defaecation (nulliparous women) or traumatic vaginal delivery (multiparous women).
- 2) Neural regeneration takes place in different patterns; perivascular nerve fibre proliferation predominates in nulliparae, collateral sprouting predominates in multiparae.
- 3) Uterine reinnervation results in dyspolar uterine contractility, dysmenorrhea, and, retrograde menstruation delivering endometrium to the pelvic cavity.
- 4) Ectopic endometrium adheres to injured peritoneal surfaces in dependent areas of the pelvis. If endometrium is not available at the time of the injury then the laparoscopic "phenotype" changes.

Table 1

The aetiology of pelvic endometriosis. Retrograde menstruation resulting from dyspolar uterine activity, and, intrapelvic injuries are the key antecedents.

According to this view, women with "endometriosis" will demonstrate; evidence of tissue injury (Fig 1b-d), uterine reinnervation (Fig 2b-d), and, dyspolar uterine contractility (Leyendecker, 1996). The portrait of a teenage, nulliparous woman with endometriosis is that she strains during defaecation, producing hypertrophic myofascial supports with fusion of rectum and vagina (Fig 1d). Their recurrent injuries result in large volumes of endometriosis (grades III/IV) at laparoscopy. The obverse occurs in multiparous women where intrapartum injuries tear myofascial supports (Fig 1b-d) that present five to ten years later, that is, after extensive reparative processes modify their appearance. Avulsion of one or both uterosacral ligaments is not unusual though more commonly asymmetrical uterosacral scarring and atrophy coexists with neovascularisation of adjacent peritoneal surfaces (Fig 1b-c). "Deep" endometriosis denotes the consequences of disruption of the uterosacral ligaments and rectovaginal septum that form the primary axis of vaginal support. Retrograde menstruation delivers endometrium to these injured surfaces though there may be little, or none, if breast-feeding, or, contraception prevents menstruation during repair of the non-recurrent, intrapartum injury.

The causes of pelvic denervation

Straining during defaecation is epidemic in Western societies (Heaton, 1993). Three per thousand women have stool frequencies of less than one per month, one per cent less than once per week (Heaton, 1993). The gender bias increases with advancing age owing to the effects of vaginal delivery and hysterectomy. Persistent straining has effects from the uterus to the vulva depending on the shape of the pelvis, or, the pattern of straining (Quinn, 2007). Stretch causes the initial denervatory injury with re-growth causing subsequent circumferential nerve fiber proliferation (Quinn, 2006, 2007). Tortuous, pelvic blood vessels escape the direct effects of straining though injuring their innervation may cause abnormal, accompanying, vascular patterns (Beard, 1984).

Allen and Masters established the original associations between intrapartum injuries, myofascial defects, and, subsequent gynaecological problems where the "postpartum cripple" suffered from a "universal joint cervix" (Allen, 1955). Their solution was to repair the fascial injuries though when Dr Allen returned to this subject he recognised hysterectomy to be an appropriate solution in some circumstances (Allen, 1971). In this second paper he drew attention to the role of premature maternal voluntary efforts and minor malpresentations in labour as sources of potential maternal injury. Recent studies confirm, and extend, these findings to include different forms of contemporary difficult intrapartum episodes

(Quinn, 2002). Swash has also recorded adjacent pudendal nerve injury from prolonged labours, heavy babies, forceps deliveries, epidurals, etc. in a sustained series of prospective studies (Henry, 1982; Snooks, 1984). The effects of somatic injury may differ in important respects from those of autonomic nerve injury.

The pathology of pelvic denervation

Cutting or tearing a nerve results in an outpouring of cytokines leading to extensive intracellular reorganisation (Makwana, 2005). Nerve cones form and axonal regeneration starts to restore lost neural functions. The usual histopathological result is expansive regenerative reinnervation (Fig 2b) where abnormal nerve fibres proliferate throughout the stroma as now described in all pelvic viscera, particularly if they are adjacent to one another (Atwal, 2005). Reinnervatory patterns result in light touch causing pain or discomfort (allodynia) whose precise mechanisms are unknown, though may describe many gynecological symptoms including some forms of vulvodynia, dyspareunia, chronic pelvic pain, dysmenorrhoea, irritative bladder and bowel symptoms (Quinn, 2002).

Persistent straining also injures pelvic nerves to produce the separate, and distinctive, neural lesion of perivascular nerve fibre proliferation (PVNFP, Fig 2d). Concentric rings of abnormal nerves enclose small arterioles partially, or completely (Atwal, 2005). It is associated with uterine, vaginal, or vulval pain appearing several years after the initial injury and sensory symptoms in the second half of the menstrual cycle. Nulliparous women presenting with sustained constipation in association with both premenstrual pelvic pain, and, premenstrual vulval pain, are not unusual. Medical treatment directed at reducing pelvic blood

flow in the second half of the menstrual cycle, or oophorectomy, can be helpful (Ling, 2000).

The site, nature and timing of uterine neural injury predicts the variable clinicopathological outcomes. Repetitive injury caused by straining to achieve defaecation injures extrinsic uterine nerves (Quinn, 2007). Traumatic vaginal delivery shears nerves as they enter the uterus resulting in collateral sprouting of nerve bundles and persistent symptoms associated with injuries to the uterus, cervix and vagina (Atwal, 2005). Injuries to the endometrial-myometrial nerve plexus resulting from curettage, endometrial ablation or unilateral neurovascular injury at Caesarean section may result in tissue proliferation across the interface in adenomyosis (Cooper 2005, Quinn, 2007). Intrapartum events may lead to intramyometrial nerve injuries resulting in formation of leiomyomas (Savitskii, 1981). Proximal injuries to autonomic nerves in the spinal cord, or in the sympathetic chain, may have pan-uterine consequences (Jasmin, 2000).

The consequences of pelvic denervation

Injuries to nerves cause loss of function, visceral dysmotility, susceptibility to infection, and pain associated with reinnervation. Women with endometriosis suffer adverse reproductive outcomes including subfertility, miscarriage, IUGR, preeclampsia, preterm labour with increased Caesarean section rates. Injury to the endometrial-myometrial nerve plexus may result in impaired decidualisation and prevent appropriate placentation producing adverse antenatal outcomes from subfertility, miscarriage, preeclampsia, IUGR, to intrapartum problems such as primary dysfunctional labour and postpartum haemorrhage (Khong, 1997).

Susceptibility to infection may promote infectious morbidity associated with recurrent urinary tract infections, vulvovaginal Candidiasis and preterm delivery. Soft tissue infection follows cutaneous denervation (Alison, 1992; Kreidstein, 1993). If the same applies to the vaginal mucosa then it offers an explanation for opportunistic infections associated with the onset of preterm labour (Goldenberg, 2008).

Sensory pelvic symptoms in adjacent organs are frequent in endometriosis. Epidemiological studies of women with chronic pelvic pain confirm high rates of coexistent sensory symptoms in anatomically-adjacent organs including irritative bladder and bowel symptoms (Zondervan, 1999). Reinnervation has been reported in different clinical syndromes in a variety of histopathological patterns

by colleagues from different clinical specialties (Christmas, 1990, Westrom 1998, Quinn 2002, Chan 2003, Tokushige 2006). Eventually new nerves infiltrate ectopic endometrium and may contribute to symptoms (Anaf, 2002).

Hysterectomy for endometriosis is frequently associated with recurrent pain within the medium term (MacDonald, 1998). Reasons for this may include persistent straining to achieve defaecation creating further neurological lesions, or histopathological changes in the dorsal root ganglia where the pain is "stored" for subsequent emergence (Jasmin, 2000).

Dyspolar uterine contractility in women with endometriosis has been described with ultrasound (Leyendecker, 1996). Women with endometriosis have more frequent subendometrial waves than controls with normal fundocervical polarity. Endometrium delivered to injured pelvic tissues has the capacity to adhere, proliferate, implant and survive particularly where oestrogen is available. Cell adhesion molecules including integrins and cadherins are abnormally expressed in endometriosis cell lines and the contents of peritoneal fluid appear to have increased invasive capacity (Koninckx, 1998).

All the elements of the denervation-reinnervation explanation of typical presentations of endometriosis, have varying degrees of support in the literature.

Diagnosis and treatment of endometriosis

If painful symptoms are directly associated with the consequences of denervation-reinnervation then early recourse to laparoscopy to establish an "accurate" diagnosis of "endometriosis" may be unnecessary in many women with chronic pelvic pain. Professional organisations recommend that clinicians consider the administration of GnRH agonists to women with chronic pelvic pain where indicated, without preliminary laparoscopic diagnosis (RCOG, 2006). This policy results from a randomised trial of GnRH agonists in women with chronic pelvic pain without a laparoscopic diagnosis, conducted by the Pelvic Pain Study Group (Ling, 2000). Most women had improved symptoms though only half had a subsequent laparoscopic diagnosis of endometriosis.

Treatment directed at preventing endometrial proliferation using oral contraceptive preparations, progestagens and GnRH agonists may be helpful irrespective of the underlying neuropathology. Perivascular nerve fibre proliferation may be particularly susceptible to temporary or permanent reductions in pelvic blood flow as afforded by GnRH agonists, aromatase inhibitors or oophorectomy. However, neuropathic pain is notoriously difficult and may "store" at higher levels in the central nervous system (Jasmin, 2000). Hysterectomy with, or without, bilateral oophorectomy, may remove most abnormal innervation and reduce pelvic blood flow respectively though medium

term studies show significant rates of recurrence of symptoms (MacDonald, 1998). Minimal access surgery may temporarily reduce symptoms though cannot expect to excise the full extent of reinnervation. Combining conventional treatment with advice to stop straining has yet to be evaluated in nulliparous women.

Prevention is both practical and achievable. Teenagers must avoid straining in the bathroom, their older sisters should avoid immoderate episodes in their first labours, and their mothers may need to consider fully the nature and extent of their proposed gynecological surgery. Intrapartum policies are more difficult to change. Reducing immoderate intrapartum manoeuvres from induction of labour to specific management of the second stage of labour, seems appropriate in the light of present knowledge. Elective Caesarean section is not the answer since injuries to nerves may result in adenomyosis and chronic pelvic pain especially with recurrent surgery.

Conclusions

Much of the pathoanatomy of endometriosis and its clinical associations are explained by the consequences of uterine denervation and injuries to myofascial supports. This view develops Sampson's theory by explaining the mechanism of retrograde menstruation, and, the pelvic injuries leading to adhesion of ectopic endometrium. Adopting this view and developing these insights will avert some of the "aetiological confusion and therapeutic anarchy" that has been the recent history of this elusive epiphenomenon.

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pain in UK primary care.**

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Figure 1

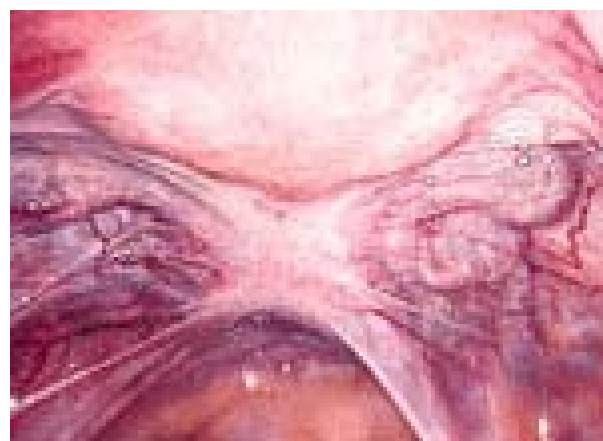
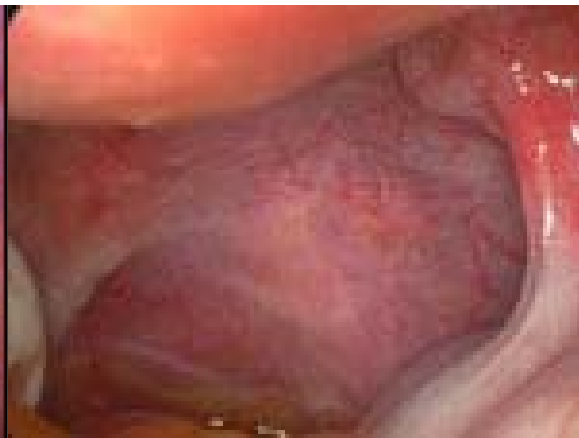
Injuries to the myofascial supports in women with chronic pelvic pain with, or without, endometriosis.

(a) normal uterosacral arch, (b) avulsion of right uterosacral ligament, (c) avulsion of left uterosacral ligament with pelvic varices, (d) symmetrical hypertrophy of uterosacral ligaments

1a



1b



1c

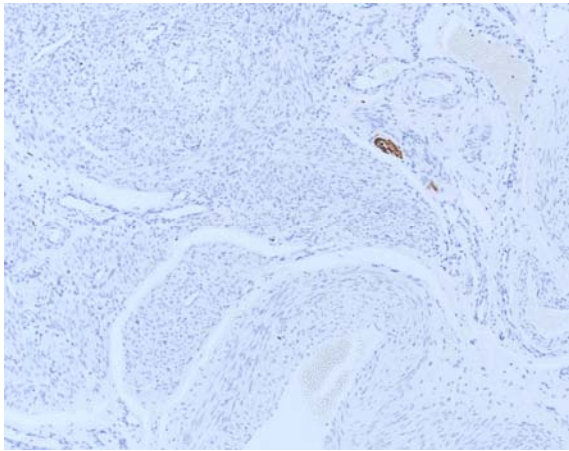


1d

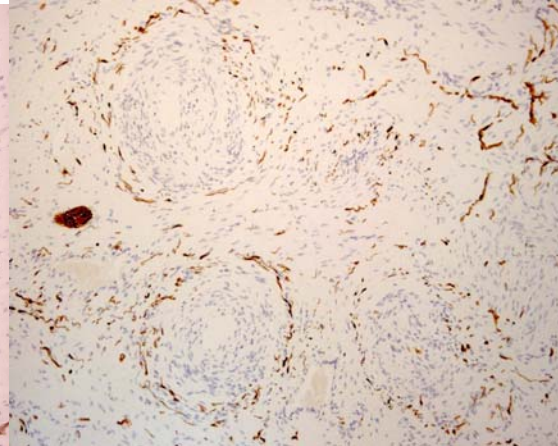
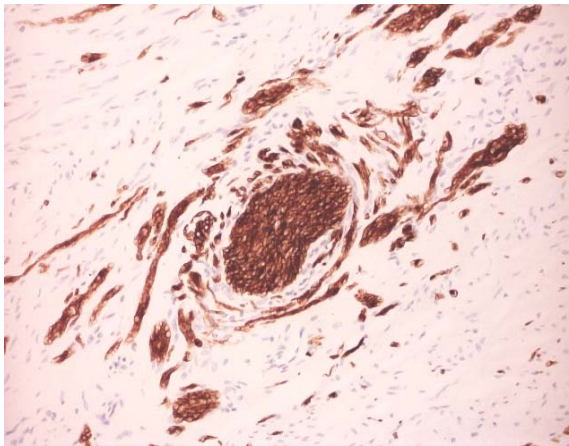
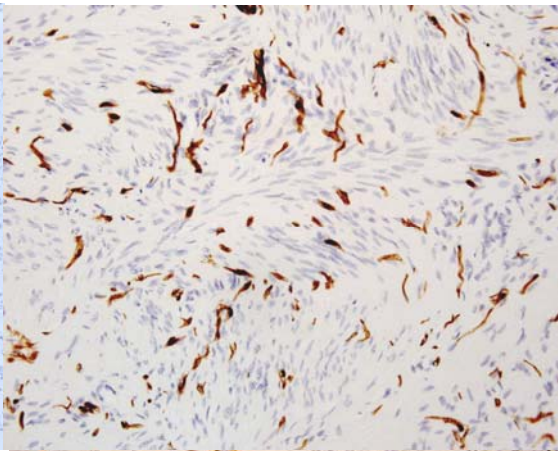
Figure 2**Different patterns of myometrial reinnervation following hysterectomy for chronic pelvic pain with, or without, endometriosis**

(a) sparsely-innervated, normal myometrium, (b) expansive regenerative reinnervation in myometrial stroma, (c) collateral sprouting of nerve bundles following traumatic intrapartum injury, (d) perivascular nerve fibre proliferation around small blood vessels (x 200).

2a



2b



2c

2d