

## Autonomic Denervation and Western Diseases

For an internist, “autonomic denervation” may suggest rare clinical situations such as Shy-Drager syndrome, Charcot-Marie-Tooth disease, or orthostatic hypotension. For a gynecologist, autonomic denervation is rapidly becoming the basis of most of our clinical work. Injuries to branches of the pelvic plexi cause endometriosis, adenomyosis, and many painful pelvic conditions, including vulvodynia, dyspareunia, and irritative bladder and bowel symptoms.<sup>1</sup> These injuries result from difficult first labors, minor gynecologic surgery requiring traction to the uterine cervix or unnecessarily vigorous curettage, and persistent straining during defecation. Latent periods of 5 to 15 years between the primary injury and the subsequent clinical presentation depend on the site, nature, and extent of the original neurologic injury. Injuries to branches of the cardiac, celiac, and pelvic plexi may contribute to clinical conditions presenting to internists?<sup>2</sup>

Burkitt and Trowell<sup>3</sup> found that Africans had lower daily stool weights (110 vs 454 g) and shorter intestinal transit times (12 vs 40 hours) than Europeans and that they did not suffer from Western diseases.<sup>3</sup> One of their students provided later epidemiologic evidence for endemic straining during defecation (30%-40%) in an urban Western population.<sup>4</sup> In that survey, 1% of women achieved successful defecation less than once per week, and, 0.3% less than once per month!<sup>4</sup> Persistent straining during defecation causes injuries to autonomic nerves with specific neurohistochemical signatures in every pelvic organ.<sup>1,2</sup> Constipated, supine infants suffer different injuries from adolescents, adults, and the elderly owing to their varying sizes, shapes, and patterns of straining. Recurrent and varying and incoordinate Valsalva maneuvers, that are all-too-obvious in the second stage of labor, may explain some cases of denervation and reinnervation in extra-pelvic organs.

Unexplained autonomic denervation and reinnervation may contribute to Western diseases through several secondary mechanisms, including visceral and ductal dysfunction, tissue hyperplasia and hypoplasia, opportunist infection, and pain and central nervous system “sensitization.”<sup>2</sup> Appendicitis, cholecystitis, pancreatitis, inflammatory bowel diseases, interstitial cystitis, allergic rhinitis, asthma, cardiac arrhythmias,

hypertension, rectal hypersensitivity, anal fissure, intervertebral disc pain, and erosive lichen planus demonstrate reinnervation in a significant proportion of patients. Some “autoimmune” conditions, including type 1 diabetes, show clear evidence of denervation of the end organ. Further swathes of morbidity result from the layered consequences of obesity, including diverse metabolic and endocrine complications, herniae, hemorrhoids, and varicose veins.<sup>2</sup>

Lower abdominal pain remains a common reason for a woman of reproductive age to consult a physician. The description of the pain often has a “neuropathic” flavor; the pain is persistent and associated with nonspecific, autonomic symptoms, such as headache, nausea, vomiting, and fainting. In the absence of “endometriosis,” generic labels such as “irritable bowel syndrome,” “fibromyalgia,” and “chronic fatigue” often find their way into the case record. In a gynecology clinic, there is almost always a clear history of a source of autonomic injury: prior difficult labor, gynecologic surgery, and persistent straining during defecation. Diagnostic laparoscopy or magnetic resonance imaging demonstrate corresponding asymmetric injuries to the pelvic supports and their associated neurovascular bundles. Neuroimmunohistochemical findings may include reinnervation in the viscus itself or its supporting ligaments.<sup>1,2</sup>

Persistent straining during defecation also results in the clinical enigma of advanced “endometriosis.”<sup>1</sup> Injuries to uterine and tubal nerves cause incoordinate dysmotility with retrograde menstruation, as well as fusion of the rectum and vagina. Adhesion of ectopic endometrium to injured pelvic tissues (eg, myofascial supports or small bowel in Crohn’s disease) causes further adhesions. Difficult vaginal delivery and traction to myofascial supports during gynecologic surgery also contribute to varying clinical phenotypes. Pain and subfertility result from these injuries rather than any effects of the macroscopic lesions of endometriosis.<sup>1,2</sup> Similar mechanisms may result in coexisting irritative bladder and bowel symptoms that may develop into some patterns of interstitial cystitis and rectal hypersensitivity.

Nineteenth century clinicians, including Lee in 1841 and Frankenhauser in 1867, produced their dissections of the pelvic and cardiac plexi in cadaveric material preserved in alcohol.<sup>5</sup> Modern undergraduate teaching takes place in formalin-embalmed cadavers. Formalin destroys autonomic nerves, not only in the great plexi of the thorax, abdomen and pelvis but also in subtle neuroanatomy in and around each viscus. This obscure neuroanatomy, together with unsuspected sources of

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injury, varying latent periods, and heterogeneous secondary mechanisms, has restricted these lines of inquiry. Temple and Burkitt<sup>6</sup> warned that we may lose several decades in our pursuit of “complex” mechanisms of disease, including genomic and epigenomic processes, before returning to consider the primary influences of diet, bowel habit, and lifestyle.<sup>6</sup> Burkitt and Trowell also suggested that most cancers were also Western diseases with similar etiological origins.

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## **Arteriolar injuries in clinical obstetric and gynecologic syndromes.**

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## Abstract

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Narrowed, uterine arterioles in the placental bed are the histologic hallmark of many, clinical obstetric syndromes including preeclampsia, IUGR, preterm labor, midtrimester loss, and, placental abruption. Early reports (1945-1980) illustrate, but do not explain, accompanying “halos” of hyalinised cells around these narrowed arterioles that are consistent features of these lesions (Fig. 1a). Similar, narrowed arterioles are common in many gynecologic syndromes where there are “halos” of regenerating, injured nerves around narrowed uterine arterioles in presentations of chronic pelvic pain, dysmenorrhea, endometriosis, dyspareunia, vulvodynia, irritative bladder, and, bowel syndromes (Fig. 1b). The neurovascular injury is one, and the same, in *both* obstetric and gynecologic, clinical syndromes. It results from injuries to pelvic vasomotor nerves (the “neural” injury) that release neural cytokines and growth factors causing transmural hyperplasia and narrowing of denervated arterioles, that become susceptible to successive, hyaline and fibrinoid changes (the “vascular” injury). Their common origins have been difficult to recognise because during pregnancy the injured arterioles extend to the placental bed, but, the injured nerves do not, leaving one, or more, layers of hyalinised cells around the injured arteriole in the placental bed biopsy (Fig 1a-b). Injuries to pelvic nerves result from “difficult” first labors, physical efforts during defecation, complications of gynecologic surgical procedures, as well as hypertension. Injuries to arteriolar vasomotor nerves induce “new” and “novel” receptors including purinergic, P2X3 and VEGF receptors in arteriolar smooth muscle that may respond to “pain” and “stretch”, or, activate other autonomic reflexes. Recent evidence suggests that the unexpectedly diverse, and varying, consequences of these neurovascular injuries may contribute to the pathophysiology of different, obstetric and gynaecologic syndromes.

**Key words:** premenstrual, pelvic pain, autonomic nerves, P2X3 receptors, VEGF receptors, hyperalgesia, allodynia.

In 1937, Drs Alan Moritz and Mary Oldt described narrowing of arterioles associated with hyperplasia of the tunica media and intima in kidney, spleen, pancreas and adrenals in a series of 100 hypertensive, post-mortem subjects (Fig. 1).<sup>1</sup> In 1945, Dr AT Hertig (Harvard, MA, 1945) described narrowed uterine arterioles in preeclampsia and placental abruption (Fig.2a).<sup>2</sup> Since those initial reports, many groups have reported similar narrowed, uterine arterioles in preeclampsia.<sup>3-7</sup> However, in many of the accompanying illustrations there are perivascular “halos” of hyalinised cells (Fig 2a) surrounding the narrowed arterioles that did not attract comment, or explanation, in the initial reports (1945 onwards). More recently, Professor Brosens and Romero have broadened the description of these narrowed arterioles to include many other important, clinical obstetric syndromes including intrauterine growth retardation, placental abruption, preterm labor, preterm PROM and midtrimester loss.<sup>8-10</sup> Narrowed uterine arterioles in the placental bed are not a specific, histologic finding.

Working independently on gynecologic tissue samples, our group described a perivascular “halo of injured nerves” in women with different forms of chronic pelvic pain with, or without, “endometriosis”, dysmenorrhea, vulval pain, irritative bladder and bowel syndromes (Fig. 2b).<sup>11,12</sup> Comparing the immunohistochemical injuries suggests that the origins of the neural and vascular (neurovascular) injuries are one and the same; however the regenerating “halo” of injured nerves is not visible in the placental bed biopsies of the obstetric syndromes because the nerves do not extend to the placental bed; they remain in the isthmus of the uterus throughout pregnancy (Fig.2a-b).<sup>13</sup> Understanding the causes and consequences of the combined neurovascular injury offers potential explanations for different, clinical, obstetric and gynecologic syndromes.

### **Early clinical accounts of uterine neurovascular injury**

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Dr HC Taylor (editor AJOG, 1953-1969) provided key insights into the etiology of premenstrual gynecologic symptoms in two series of patients that he studied in the 1940-50's.<sup>14-18</sup> He thought the origins of the symptoms were “a disorder of the pelvic autonomic nervous system with a vascular component, occurring in psychiatrically predisposed individuals”.<sup>15</sup> He, further, suggested there was a “tendency to hyperalgesia in different areas of the pelvis supplied by the sensory components of visceral nerves”. Dr Taylor offered the deterioration of symptoms in the week before the onset of menstrual flow, their provocation by sexual intercourse, and, the finding of distended veins and amber fluid in the pouch of Douglas, as “clear evidence of a vascular disorder”.<sup>18</sup> Dr WM Allen (St Louis,

MO), recorded similar findings at laparotomy in a smaller group of 28 patients with chronic pelvic pain, though he emphasised the accompanying, traumatic laceration of myofascial supports, notably the uterosacral ligaments (Fig.2).<sup>19,20</sup> In his 1955 paper,<sup>19</sup> Dr. Allen recorded chronic pelvic pain following a prior, significant, obstetric event in 22/28 cases, and occasionally, following cases of abortion and constipation (*vide infra*). At laparotomy, he made similar observations to Dr Taylor, describing amber fluid in the pouch of Douglas, unilateral or bilateral avulsions to the uterosacral and broad ligaments, along with uterine retroversion. Initially, he attempted to repair the myofascial injuries but reverted to hysterectomy after disappointing results.<sup>20</sup> In that second report, Dr Allen suggested that these injuries were sustained, for the most part, during difficult, intrapartum events. He had identified both the source and anatomic site of a putative, neural injury long before the widespread availability of laparoscopy and advanced, cross-sectional imaging techniques.

### Obstetric and gynecologic “syndromes”

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Professors Brosens and Romero have subsequently drawn attention to the association of the “great” obstetric syndromes with defective deep placentation, namely, the presence of “obstructive lesions” in the myometrial segments of the spiral arteries.<sup>5-10</sup> These collated reports describe similar, non-specific, vascular changes in preterm labor, preterm premature rupture of the membranes, placental abruption and midtrimester abortion.<sup>8-10</sup> Much attention has been given, historically, to events taking place *during* pregnancy including “mechanisms of endovascular trophoblast invasion” though less attention given to potential injuries taking place *before* pregnancy.

Our group has drawn attention to the similarity of the histologic appearances in gynecologic syndromes in chronic pelvic pain, “endometriosis”, vulval and vaginal pain, irritative bladder and bowel syndromes.<sup>21-30</sup> In all these syndromes the histologic appearances include perivascular nerve fiber proliferation (PVNFP) where there are one, or more, layers of injured, regenerating nerves around narrowed arterioles (Fig. 1b-d).<sup>21</sup> Importantly, these may arise as a consequence of physical efforts during defecation, or, prolonged maternal voluntary efforts in the second stage of labor (among other obstetric injuries); both of which may lead to different, gynecologic syndromes.<sup>21,29</sup> Other groups have described denervation-reinnervation in different pelvic organs and syndromes,<sup>31-39</sup> including endometriosis,<sup>40-50</sup> though without necessarily describing the source of these injuries.

## The pelvic autonomic nerves

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Robert Lee described the morphology of the pelvic autonomic nerves in 1840, amidst considerable controversy.<sup>51-53</sup> Few of his colleagues, believed that they were looking at nerves in his prosections in alcohol (Fig. 3). Not every contemporary colleague will be familiar with the detailed morphology of the pelvic autonomic nerves as they converge on the vaginal vault where they are vulnerable during difficult labors, gynecologic surgery requiring incision of, or, traction to the cervix, and, physical efforts during defecation (Fig.3).<sup>54</sup> Post-1945 generations of medical students have been taught on cadavers embalmed in formalin that destroys, rather than demonstrates, autonomic nerves. The sympathetic (T10-L2) and parasympathetic nerve fibers (S2-4) pass through the uterosacral and broad ligaments in two key nerve bundles; the first runs through the uterosacral ligaments to supply the nerve plexus at the endometrial-myometrial nerve plexus; the second bundle enters the uterus with the uterine artery to supply the subserosal plexus. Both converge on a tubal plexus that supplies the proximal two thirds of the Fallopian tube whilst the distal third receives nerves from the ovarian plexus through the free edge of the mesosalpinx.<sup>55</sup> Ampullary ectopic pregnancy often arises from normal oocyte “pick-up” by the fimbriae but failure to transport the embryo along the Fallopian tube owing to an ipsilateral injury to the nerve supply of the proximal two thirds that is usually visible in the ipsilateral uterosacral ligament.<sup>28</sup> Recognising injuries to autonomic nerves as the source of clinical obstetric and gynecologic syndromes may have been impaired by loss of their morphology in formalin-embalmed cadavers however there has also been a problem with their microscopy. In Fig 1. Row 4b, there is a pancreatic nerve bundle demonstrating a “cutting artefact” on its superior border however there is clearly accompanying loss of at least four longitudinal nerve fibers in the nerve bundle. Many pathologists have collectively labelled these appearances as coincidental “cutting artefacts” when the loss of longitudinal nerve fibers is, in fact, a key indicator of distal denervation in that tissue section.

## Causes of neural injury in the female pelvis

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### (a) Childbirth

“Difficult”, nulliparous labors result in chaotic, neural injuries with both perivascular nerve fiber proliferation, and, some degree of stromal reinnervation (Table 1). Regenerating nerves re-grow over 4-5 years and become dense enough to result in hyperalgesia (or, allodynia) where “light touch causes pain or discomfort”.<sup>56</sup> Aberrant reinnervation has been described in every pelvic organ and

some patterns of vulvodynia, dyspareunia, dysmenorrhea, frequency and urgency in response to bladder filling, or, irritative bowel symptoms, correspond to this formulation. In 2420 nulliparous women in the Avon Longitudinal Study of Pregnancy and Childbirth (ALSPAC, 1992) dataset there was doubling of self-assessed, “severe” gynecologic symptoms including chronic pelvic pain at 47 months post-delivery in women who had undergone “difficult” first labors (Table 1).<sup>57</sup> That figure may significantly understate the size and extent of subsequent gynecologic problems since most women with chronic pelvic pain do not present until 5-8 years after their first baby. The laparoscopic phenotypes of parous women with chronic pelvic pain often demonstrate asymmetric, “traumatic laceration” of their myofascial supports, with, or without, deposits of ectopic endometrium (Fig. 3). If the mother breastfeeds for six months then there will be no endometrium to adhere to asymmetric, pelvic myofascial injuries whereas if she bottle feeds then there may be ectopic endometrium available to define the injury.<sup>58</sup> There are often, similar, extensive neural injuries in the uterine isthmus and adjacent anatomic structures, irrespective of deposits of ectopic endometrium, though even these deposits of endometrium will develop reinnervation in mature lesions, justifying a surgical approach to some of these patients problems.<sup>41-43</sup>

#### **(b) “Constipation”**

The relationship between some aspect of “constipation” - carefully defined, in this account, as “persistent, physical efforts during defecation” – and subsequent Western diseases, has a long, and controversial history. Sir William Arbuthnot Lane, Bt, wrote an important account of “chronic intestinal stasis” and its treatment by colectomy in 1924 however there have been subsequent, important physiologic contributions by DP Burkitt, FRS, epidemiologic studies by KW Heaton, FRCP, and, demonstration of immunohistochemical consequences by our group.<sup>21,59-62</sup> One percent of urban, Western populations only achieve defecation once per week, and, 0.1% only achieve defecation once per month.<sup>62</sup> Worse still, 20-30% percent require physical efforts to start or finish defecation;<sup>62</sup> it is these physical efforts that cause “longitudinal” injuries to uterosacral ligaments (Fig 3a-d), and, autonomic nerve bundles that result in regeneration of new injured nerves (“autonomic neurapraxis”).<sup>21</sup> In nulliparous women with organ-specific, premenstrual symptoms e.g. dysmenorrhea, vulval pain, vaginal pain, irritative bowel and bladder syndromes there is a common histologic lesion that is caused for the most part, by a single neurologic injury (Fig.1b).<sup>21,29</sup> These “new” nerves create concentric layers of injured nerves around pelvic arterioles maintaining close relationships with the adjacent, denervated and narrowed arteriole.<sup>21,23,29</sup> Increases in pelvic blood



flow typically cause premenstrual pain that we label as different, clinical syndromes depending on the organ that has been injured (Fig. 1b).<sup>31-39</sup>

### **(c) Gynecologic surgery**

The third cause of injuries to pelvic autonomic nerves is gynecologic surgery, most frequently, medical or surgical evacuation of the uterus.<sup>63,64</sup> Excessive traction to the cervix during surgical evacuation results in injuries to the uterosacral ligaments whereas hyperstimulation associated with administration of prostaglandins, or oxytocic agents, causes a similar injury to uterine nerves.<sup>64</sup> Over-vigorous curettage may also injure the nerve plexus at the endometrial-myometrial nerve plexus.<sup>30</sup> Clearly any surgical procedure that divides pelvic nerves may be the source of subsequent neurologic symptoms including LLETZ, cone biopsy, hysterectomy, colporrhaphy, etc. The key to understanding their pathophysiology is recognising the diverse and varying consequences of these autonomic injuries (Table 2).

### **(4) Hypertension**

Sustained high, intravascular pressures cause characteristic, pre-pregnancy injuries to uterine arterioles (Fig. 2).<sup>65,66</sup> Typically, there is aberrant reinnervation of injured vasomotor nerves though the histologic appearances differ slightly from the smooth “halo of hyalinisation” in Fig. 2a. Instead of the smooth layer of hyalinisation there is a more disorganised appearance that looks like “woven baskets” surrounding the narrowed arterioles (Fig. 2c). Similar appearances are apparent in other viscera including the kidney (Fig.1 Row 2b). These appearances are identical to those arising in the uterus in preeclampsia and other obstetric syndromes. Furthermore, it is now clear that women suffering from sustained preeclampsia, that causes fixed injuries to renal vasomotor nerves, may develop hypertension within a few years of their deliveries along with the potential for severe cardiovascular morbidity owing to the fixed injury to their renal circulation.<sup>67</sup> Attitudes to the timing of delivery in the hypertensive disorders of pregnancy may need to take into account the risks of remote consequences for the mother?

## **Consequences of neural injury in the female pelvis**

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Injuries to autonomic nerves carry a surprisingly wide range of pathophysiologic consequences (Table 2). In the uterus there is clear evidence of different patterns of endometrial hyperplasia

(adenomyosis)<sup>30</sup> and myometrial hyperplasia (leiomyoma)<sup>68-70</sup> associated with different patterns of neural injury to the endometrial-myometrial nerve plexus and myometrium respectively, whereas in non-estrogen-sensitive tissues e.g. bladder and bowel, similar injuries result in atrophy. Uterotubal dysmotility results in retrograde menstruation, dysfunctional labor, subfertility and ectopic pregnancy.<sup>12,27,28</sup> Denervation of mucous membranes results in opportunist infection leading to a range of gynaecologic infection as well as contributing to some forms of preterm labor and PPROM.<sup>71</sup> Uterine arteriolar stenosis impairs fetal growth and injuries to vasomotor nerves cause viscerovisceral reflexes (uterorenal, hepatorenal and lienorenal) that cause cardiovascular adjustments that may result in preeclampsia, HELLP syndrome, and, subsequent, early-onset, postpartum hypertension.<sup>71</sup> Injured uterine nerves express TRPV-1 “pain” receptors, and, induce purinergic (P2X3) “stretch” and VEGF receptors in myometrium and arteriolar smooth muscle that may contribute to different patterns of vulvodynia, vaginal pain, chronic pelvic pain, irritative bladder and bowel syndromes, etc as well as central sensitisation leading to recurrent pain following surgery e.g. hysterectomy.<sup>72</sup> Viscerovisceral reflexes may also account for extrapelvic autonomic symptoms wherever there has been activation of pelvic autonomic injuries.<sup>73</sup> Many non-pregnant women with premenstrual syndromes may have dramatic extrapelvic symptoms in the week before menstruation owing to activation of injured nerves by increases in pelvic blood flow, whereas the weight of the pregnant uterus at 16-20 weeks gestation may contribute to pelvic pain with accompanying extrapelvic symptoms in multiparous women 4-5 years after a “difficult” first labor (Table 1).

### Neurovascular origins of some gynecologic syndromes

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Leiomyoma, adenomyosis and endometriosis all carry neurologic injuries. Savitskii described loss of nerves in some patterns of acquired leiomyoma in three papers in the 1980's.<sup>68-70</sup> Diffuse, symmetric adenomyosis arises from loss of nerves at the endometrial-myometrial interface associated with bilateral injuries to the uterosacral ligaments (Fig. 2a-d).<sup>74</sup> Less dramatic, neural injuries may cause different patterns of adenomyosis at different uterine sites as originally described by Thomas Cullen in 1908.<sup>75</sup> Different patterns of “endometriosis” are associated with injuries to uterovaginal nerves that cause retrograde menstruation with adhesion of ectopic endometrium to sites of tissue injury e.g. symmetric, hypertrophied, uterosacral ligaments following years of physical efforts during defecation, or, asymmetric, attenuated, uterosacral ligaments following difficult intrapartum episodes.<sup>40-49</sup> The laparoscopic appearances are both, dichotomous and confusing – but if the surgeon ignores the

ectopic endometrium, notes the myofascial injuries, and, asks the question “What injuries has this woman sustained, and, when did they occur?” then (s)he may be able to provide a better explanation of their origins with improved advice to the patient<sup>76</sup> Both uteri demonstrate aberrant reinnervation throughout the anatomic structures at the junction of uterus and vagina that may include the isthmus of the uterus, cervix, upper vagina, uterosacral-cardinal ligaments, peritoneal surfaces and, even, the ectopic endometrium, itself.<sup>29,40-49</sup> The prevailing opinion remains that deposits of ectopic endometrium are the primary source of pelvic pain; though some believe that increases in pelvic blood flow on regenerating nerves expressing “new and novel” pain receptors may be a better explanation of symptoms. Vulvodynia, dyspareunia, dysmenorrhea, irritative bladder and bowel syndromes are all definable as “light touch causing pain or discomfort”, and, associated with different patterns of injury to pelvic nerves with similar pathophysiologic consequences and outcomes.<sup>30-39</sup>

### **Neurovascular origins of some obstetric syndromes**

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Recognising that the neurovascular injury in the placental bed in the obstetric syndromes also results from injuries to uterine nerves is an important insight that may redirect etiologic attention in some of the common obstetric syndromes (Fig. 1a-b).<sup>8-10,71</sup> Denervatory injuries to smooth muscle of arterioles and myometrium induces primitive, purinergic, P2X3 receptors that use ATP as a neurotransmitter (Fig. 1e-f).<sup>77</sup> Stretching injured tissues including denervated arterioles releases ATP that stimulates reflex activity through uterorenal nerves that, in turn, causes a renal cortico-medullary vascular shunt.<sup>71</sup> Shutting down blood flow to the renal cortex activates the renin-angiotensin system and results in “early-onset” preeclampsia – that may be prevented, in part, by early administration (pre-16 weeks) of aspirin (Fig. 4a-d).<sup>71,78</sup> Stretching injured myometrium may result in “late-onset” preeclampsia that is not prevented by aspirin.<sup>71</sup> Loss of uterorenal nerves as a result of sustained physical efforts during defecation may result in intrauterine growth retardation without activation of the uterorenal nerves, hypertension and proteinuria.<sup>71</sup> Denervation at any site in the lower genital tract will create the conditions for opportunist organisms to contribute to PPROM and preterm labor, and, rupture of the fibrinoid or hyaline “degenerations” of these vessels may result in placental abruption.<sup>71</sup> All are possible consequences of the original neurovascular injury.<sup>11,12</sup> As previously discussed, similar neurovascular injuries take place in kidney, spleen, adrenal and pancreas in hypertensive individuals,<sup>1,65,66</sup> and, may contribute to the development of HELLP syndrome during pregnancy and early-onset, postpartum hypertension that leads to significant cardiovascular events.<sup>67</sup>

## Conclusions

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Many clinical, obstetric and gynecologic syndromes develop from the remote consequences of autonomic neurovascular injuries. Injuries to pelvic vasomotor nerves result from “difficult” first labors, physical efforts during defecation, complications of common gynecologic, surgical procedures and hypertension. Clinical presentations depend on the site, nature and extent of the injury. In the UK, uterotubal neurovascular injuries frequently occur during “difficult” first labors and straining during defecation leading to “partial” injuries to nerve bundles that permit a pathway for regenerating injured nerves and subsequent *painful*, clinical syndromes of chronic pelvic pain, painful periods, painful sex, vulval pain, irritative bladder and bowel syndromes. In China, injuries to these pathways during midtrimester abortions tend to cause “complete” avulsion of the nerve bundles in the uterosacral ligaments leading to *painless* clinical presentations of infertility, ectopic pregnancy, and, advanced “painless” adenomyosis.

Preventing these neural injuries is clearly important since there appear to be few barriers to regenerating injured nerves that may cause pain and suffering at different times of life. Encouraging breastfeeding and appropriate toilet-training to establish a reliable infant diet and bowel habit are significant, preventive tasks. In the reproductive years, neuroprotective, intrapartum care and carefully-considered approaches to common gynecologic surgical procedures, are clearly important preventive approaches. Many post-reproductive careers continue to be marred by the direct, and indirect, consequences of childbirth decades after the original injuries. Preventing autonomic neurovascular injury becomes an important aspect of maintaining womens reproductive health and well-being over the course of their lifespans.

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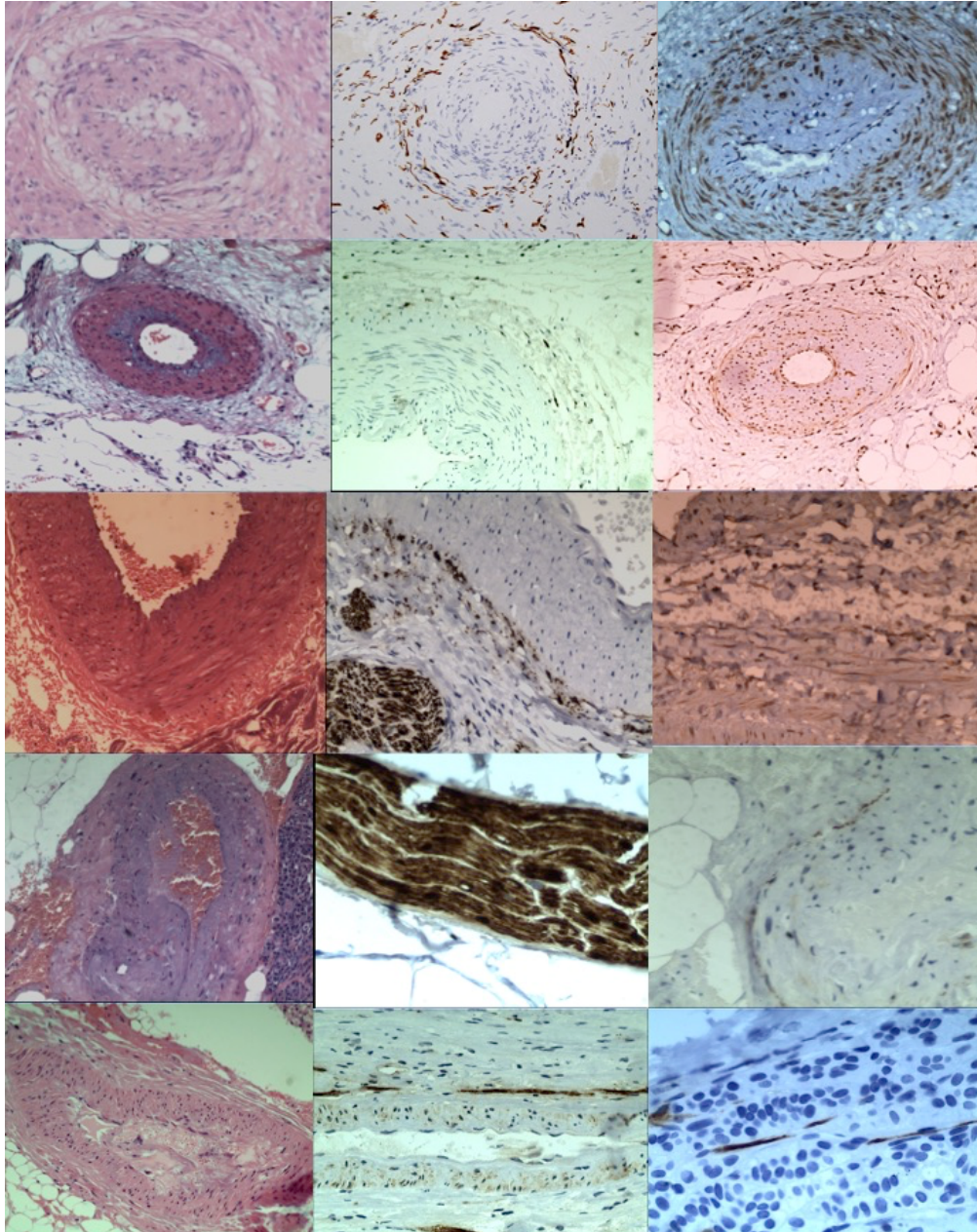
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**Fig. 1 Visceral arteriolar injuries in pregnant, and, non-pregnant, hypertension.**

(a) H&E

(b) anti-S100

(c) anti-P2X3



Widespread visceral arteriolar stenosis in hypertension was originally described by Dr A Moritz & M Oldt, 1937 (Cleveland, OH.) in kidney, spleen, pancreas and adrenals (2-5 A-C), though similar injuries may take place in the uterus in preeclampsia (1A-C) with, or without, HELLP syndrome .

Row 1 uterus, Row 2 kidney, Row 3 spleen, Row 4 pancreas, row 5 adrenals,

Column (A) is stained with hematoxylin and eosin, Column (B) is stained with anti-S100 antibody, Column (C) is stained with anti-P2X3 antibody.

Row 1a shows narrowed uterine arteriole with a “halo of hyalinisation” in the obstetric syndromes (x100, HE)

Row 1b shows narrowed uterine arteriole with a “halo of injured nerves” in the gynaecologic syndromes (x100, anti-S100)

Row 1c shows narrowed uterine arteriole expressing P2X3, purinergic receptors in hyperplastic tunica media and intima (x100, anti-P2X3)

Row 2 a-c shows narrowed arterioles from the hilum of the kidney demonstrating injured, perivascular renal nerves and early expression of P2X3, purinergic receptors in hypertension.

Row 3a-c shows narrowed arterioles from the hilum of the spleen demonstrating multiple layers of injured *perivascular* nerves (x100 Fig.1.iii.b)

Row 4a-c shows narrowed arterioles from the pancreas including a pancreatic nerve bundle with a U-shaped “cutting artefact” in its superior border as well as authentic *loss* of nerve fibers throughout the nerve bundle.

Row 5a-c shows narrowed arterioles from adrenals demonstrating adrenal cortical hyperplasia at x100 and x200 associated with injured pericortical nerves in this specific form of hypertension. Compare with denervatory endometrial and myometrial hyperplasia in adenomyosis and leiomyoma respectively.

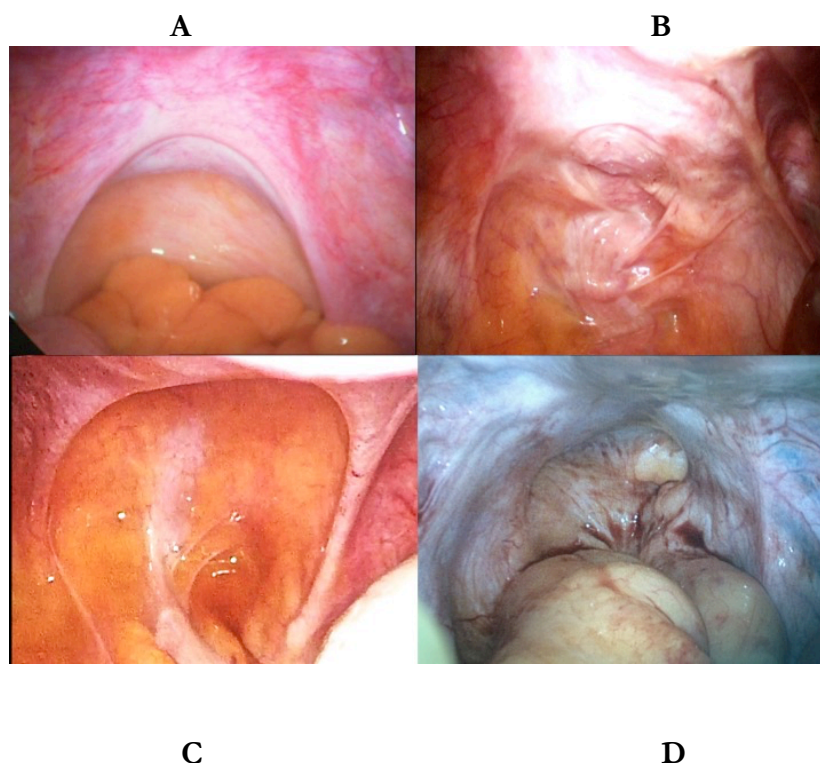
**Figure 2** The pelvic autonomic nerves prosected and preserved in alcohol (not formalin) as described by Robert Lee, 1841 and Franz Frankenhauser, 1867



The pelvic autonomic nerves converge on the vaginal vault where they are vulnerable to injury during prolonged and persistent physical efforts during defecation, difficult first labours, and, some forms of gynaecologic surgery e.g. evacuation of the uterus. Pelvic sympathetic nerves (T10-L2) pass through the superior hypogastric plexus (1), hypogastric nerve (2), inferior hypogastric plexus (3), to enter the uterovaginal plexus of Frankenhauser (4), in combination with pelvic parasympathetic nerves from sacral segments S2-4 (5).



**Figure 3** Different patterns of injuries to the uterosacral ligaments in different clinical circumstances, similar to myofascial injuries described originally by Dr WM Allen & Dr W Masters, 1955 (St Louis, MO).



A = normal, nulliparous, uterosacral ligaments contain uterine and tubal nerves that supply the endometrial-myometrial nerve plexus and the proximal two thirds of the Fallopian tubes

B = asymmetric injuries to uterosacral ligaments with, on the left, complete avulsion of uterine and sacral origins, and, on the right, scarring of the uterine insertion and probable, avulsion of sacral origin. These are typical of asymmetric forces during vaginal delivery.

C = symmetric injuries to uterosacral ligaments with bilateral avulsions of sacral origins. These, unusual appearances are typical of excessive uterine activity in early pregnancy e.g. following administration of misoprostol for miscarriage or unwanted pregnancy. Attenuation of the ligaments, without clear avulsion typically occurs following excessive uterine activity after administration of prostaglandins or intravenous oxytocin.

D = complete absence of uterosacral ligaments. These appearances are unusual in Western gynaecology though is not uncommon in China during the “one-child” policy. These injuries usually follow one, or more, second trimester abortions; they result in infertility, ectopic pregnancy or diffuse, symmetric adenomyosis in later life.

**Table 1**                      **Causes of injury to pelvic autonomic nerves**

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- (1) **“Difficult” first labors** double the risk of “self-assessed “severe” gynecologic symptoms at 47 months post-delivery. The clinical associations with this risk include:
  - Induction of labor
  - Prolonged labor (> 12 hours in the active phase)
  - Prolonged maternal voluntary efforts (> 2 hours)
  - Fetal weight > 4000g
  - Malpresentations e.g. occipitoposterior position
  - Operative vaginal delivery
  
- (2) **“Constipation” specifically, persistent voluntary efforts to achieve defecation**, usually in the sitting position (squatting prevents recurrent straining maneuvers). In the female pelvis it is most common in nulliparous presentations of chronic pelvic pain with, or without, endometriosis, vulvodynia, vaginal pain”.
  
- (3) **Complications of evacuation of the uterus**
  - (a) Excessive traction to the cervix and uterosacral ligaments resulting in injuries to the contained, uterotubal nerves (Fig. 4B)
  - (b) Over-vigorous curettage resulting in injuries to the endometrial-myometrial nerve plexus that lies less than one millimetre beneath the endometrial-myometrial interface
  - (c) Excessive uterine activity resulting from administration of misoprostol leading to thinning and attenuation of uterosacral ligaments with injuries to the contained, uterotubal nerves (Fig.4c). Prostaglandins and oxytocic agents may cause similar injuries
  
- (4) **Other gynecologic surgical procedures** that divide nerve bundles including LLETZ, cone biopsy, colporrhaphy, hysterectomy, etc.
  
- (5) **Hypertension** causes injuries to pelvic vasomotor nerves with narrowing of adjacent arterioles leading to visceral stenosis, ischemia and thrombosis in different clinical situations



**Table 2                      Consequences of injury to pelvic autonomic nerves**

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**(1) Changes in shape and size of the viscus**

Neural injury in estrogen –sensitive tissues has different effects from non-estrogen-sensitive tissues. Myometrial injury may result in myometrial hyperplasia in leiomyoma, whereas injuries to the endometrial-myometrial interface may result in painless or painful, adenomyosis. Neural injury in bladder and bowel leads to atrophy.

**(2) Changes in visceral function**

Injuries to uterotubal nerves are associated with uterotubal dysmotility in chronic pelvic pain with, or without, “endometriosis”, adenomyosis and ectopic pregnancy.

**(3) Arteriolar stenosis, ischemia and thrombosis**

Injuries to vasomotor nerves may lead to release of cytokines and growth factors resulting in arteriolar stenosis, ischemia and thrombosis e.g. some patterns of intrauterine growth retardation

**(4) Visceral denervation of mucous membranes** leading to “opportunistic” infection e.g. vulvovaginal Candidiasis, preterm labor, etc

**(5) Aberrant reinnervation** leading to chronic pelvic pain and demonstrated in all pelvic organs in different painful or irritative conditions.

**(6) Viscerovisceral reflexes** following injuries to autonomic nerves e.g. the uterorenal reflex in preeclampsia, hepatorenal and cardiorenal syndromes, some extrapelvic manifestations in premenstrual syndrome

**(7) Chronic pelvic pain** leading to sensitisation of the central nervous system including posthysterectomy pain, and other forms of postsurgical pain.