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Autonomic denervation: A new aetiological framework for clinical obstetrics and gynaecology

M.J. Quinn

Department of Obstetrics & Gynaecology, First Affiliated Hospital, Medical University of Wenzhou, Wenzhou 325000, PR China

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ABSTRACT

The hypothesis is that many clinical conditions in obstetrics and gynaecology result from the diverse and varying consequences of injuries to pelvic autonomic nerves. These injuries result from difficult first labours, persistent physical efforts during defaecation, and, medical and surgical techniques for evacuation of the uterus. The neuro-immunohistochemical "signatures" of these injuries are variations of the Dixon–Robertson–Brosens (DRB) lesion in preeclampsia, where there is hyperplasia of the tunica intima and media of arterioles with narrowing of the lumen of the vessel. In stage IV, nulliparous "endometriosis" (and other gynaecological conditions) there are circumferential layers of abnormal nerves around a narrowed arteriole, whereas in early-onset preeclampsia (and other obstetric conditions) there are similar histological findings in uterine arterioles but there is no sign of injured nerves. During pregnancy there is elongation of blood vessels but no elongation of injured nerves leading to relative denervation of the myometrium. These lesions are detectable in most of the "great" obstetric syndromes, and, across the spectrum of gynaecological syndromes. They provide a coherent explanation of the natural history and clinical presentations of many of these syndromes. Clinical features vary with the site, nature and extent of the injury; a minor injury may enable pregnancy though it is complicated by late-onset preeclampsia whereas a more extensive injury may prevent pregnancy and present with chronic pelvic pain with, or without, endometriosis.

The hypothesis raised in this paper is that many clinical conditions in both obstetrics and gynaecology result from the diverse and varying consequences of injuries to pelvic autonomic nerves. Most obstetric and gynaecological conditions are syndromes i.e. collections of symptoms and signs that have no delineated causes. This paper suggests that the underlying lesion in "early-onset preeclampsia" is similar to that in advanced, nulliparous "endometriosis"; the difference between the two conditions being the site, nature and extent of the neurological injury. This hypothesis draws attention to the similar histological findings across "labelled" obstetric and gynaecological syndromes, and, sets out the causes and consequences of those injuries.

In 1840, Robert Lee described the detailed anatomy of the cardiac and pelvic autonomic plexi in specimens preserved in alcohol [1]. In the intervening years clinical medicine "lost" the full morphological anatomy of the "great" autonomic plexi – largely because increasing numbers of post-1945 medical students required cadavers preserved in formalin rather than alcohol to preserve their educational "life" [2]. Formalin destroys autonomic nerves. These autonomic plexi and their branches have been "out of sight, and, out of mind" in post-1945 clinical medicine though the consequences of their injury may account for much of reproductive ill-health and many, Western diseases [3].

The uterus receives nerves through the uterosacral ligaments that supply the endometrial-myometrial nerve plexus, and, with the uterine artery that supply the subserosal plexi and myometrial "pump". The muscle layers of the Fallopian tubes receive nerves from the uterus, via the mesosalpinx, and, from the ovarian plexus that supplies the distal third of the tube including the fimbriae [4]. Injuries to uterine nerves resulting from difficult first labours, surgery, drugs and persistent physical efforts during defaecation (endemic in Western societies) cause much female reproductive ill-health [3,5]. They may also contribute to many Western diseases through a series of wide-ranging and unpredictable consequences that vary with the relationship between the nerves and the organ they supply, the shape and size of their owner, and, their pattern of physical efforts during defaecation [5].

Causes of injuries to pelvic autonomic nerves

Professor Sir Dugald Baird said the "vast majority of gynaecological symptoms arise from injuries or infections sustained in

E-mail address: mjquinn001@btinternet.com

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Table 1
Obstetric interventions associated with doubling the risk of "severe" gynaecological symptoms at 47 months in 2240 primigravid women in the ALSPAC dataset (ALSPAC, 1992). Premature (before full dilatation) and prolonged maternal voluntary efforts (greater than 2 h) may also be associated with avulsion of the bilateral origins of levator ani from the obturator internus on MR imaging.

Induction of labour
Prolonged labour (>12 h in active labour)
Prolonged second stage of labour (>2 h, maternal voluntary efforts)
Fetal macrosomia (>4000 g)
Operative vaginal delivery
Malpresentations

childbirth". A prospective study of 2240 nulliparous women at 4 years after delivery finds doubling of the rates of "severe" gynaecological symptoms associated with different clinical interventions ([6], Table 1). Subsequently, there are three, distinctive sources of injury to uterine nerves: (i) difficult first labours, [2] persistent physical efforts during defaecation, [3] gynaecological surgery [5]. These produce two distinctive neurological lesions; (a) collateral sprouting of nerve bundles that forms traumatic "microneuromas" ([7], Fig. 1a & b), and, (b) perivascular nerve fibre proliferation (PVNFP, Fig 1c and d) in every pelvic organ associated with chronic pelvic pain or irritative gynaecological symptoms (Table 2). Both patterns of injury may coexist though one or other tends to dominate based on the original source of the neural injury.

In the UK, difficult first labours account for the overwhelming proportion of neurological injuries whilst subsequent vaginal deliveries may delay the clinical presentation of symptoms until the first child is aged 7 or 8 years of age [7]. The latent period varies with the site, nature and extent of the initial injury – which may include several pelvic organs –, the number of subsequent pregnancies, and, the individual woman. The consequences to a womans' reproductive health at 10 years after different obstetric interventions are not known. Serious risks of 10–20 years of chronic pelvic pain, menstrual problems, irritative bladder and bowel symptoms, vulval pain and recurrent infection, and, their attendant gynaecological surgery, seem important considerations that require discussion during a womans' first pregnancy before she goes into labour?

Most forms of major gynaecological surgery injure pelvic nerves and undermine the support of pelvic organs. However, surgical evacuation of the uterus at miscarriage and termination of pregnancy carry particular risks since excessive traction to the uterus avulses the uterosacral ligaments and over-vigorous curettage injures the nerves at the endometrial-myometrial interface [8]. In China, recurrent and late, terminations cause widespread injuries that result in infertility and ectopic pregnancy in their 20's, and, advanced painless adenomyosis in their 40's [9–11]. Medical treatment with mifepristone and misoprostol may cause excessive uterine activity that destroys the uterosacral ligaments and mesosalpingeal nerves resulting in similar morbidity [9]. Similar

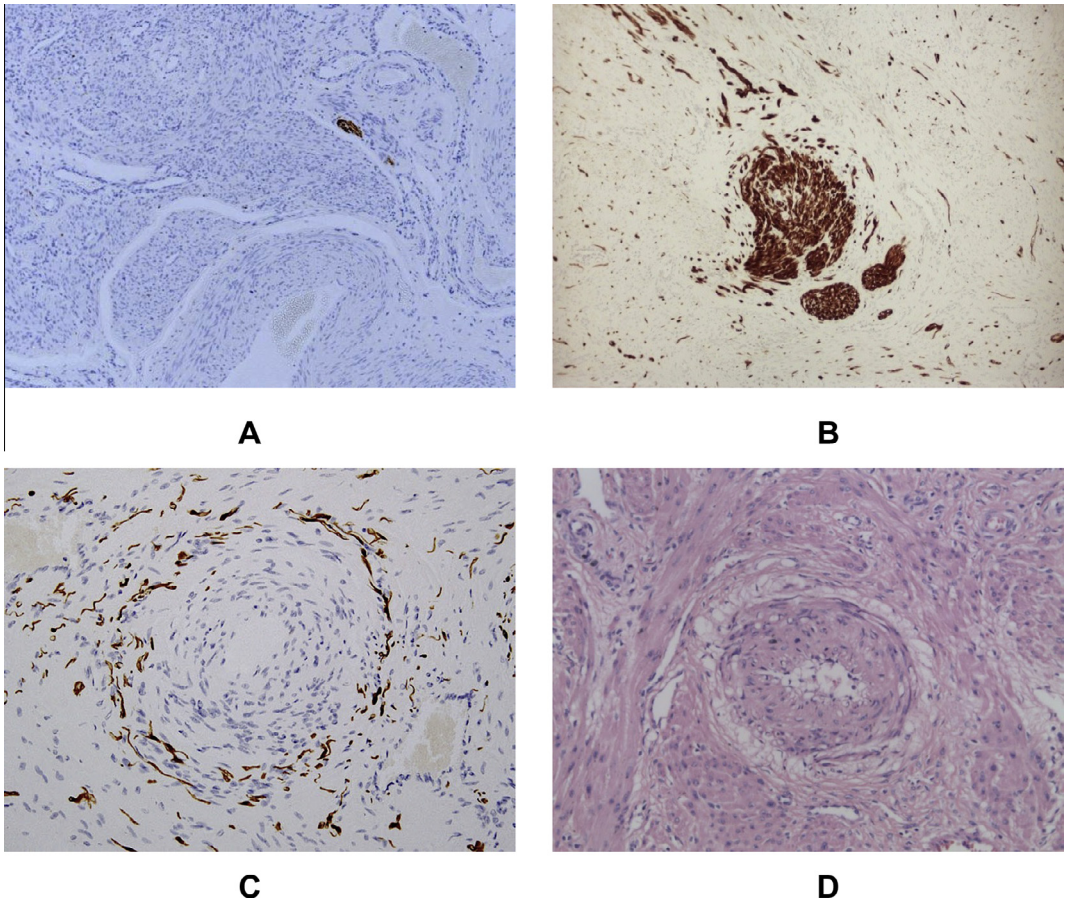

Fig. 1. (a) the normal myometrium has sparse neurovascular bundles (Stained with anti-S100, objective ×10), (b) collateral sprouting of nerve bundles is pathognomonic for traumatic injury to the nerve bundle (Stained with PGP 9.5, objective ×20), (c) hyperplasia of the tunica media and intima of a uterine arteriole in the uterine isthmus with a halo of injured and abnormal nerves. Cytokines released by injured vasomotor nerves cause proliferation of both nerves and denervated vessel walls. Similar lesions are seen in a wide range of gynaecological presentations. (Stained with PGP 9.5, objective ×20), (d) the Dixon–Robertson–Brosens lesion in preeclampsia was originally described as a "degenerative arteriolitis" with hyperplasia of the tunica intima and media, there are no injured nerves around the vessel as nerves do not elongate during pregnancy whereas blood vessels can do so under the influence of oestrogen, (Stained with H&E, objective ×20).

Table 2
Some of the consequences of injuries to autonomic nerves in the lower genital tract and possibly other anatomical sites throughout the body.

Changes in visceral form	Benign hyperplasia of the myometrium (leiomyoma), and endometrium (adenomyosis)
Changes in visceral function	Failure of productive functions of the organ e.g. insulin in the pancreas
Changes in visceral motility	Injuries to the nerve supply of the muscle of the organ or their ducts; e.g. Fallopian tube in ectopic pregnancy, or, endometriosis
Sensitivity to infection	Denervation of mucosal surface creates an increased. sensitivity to infection; e.g. bacterial vaginosis, Candida
Sensitivity to other toxins	Breaches in the autonomic nervous system often make the individual more sensitive to exogenous toxins; e.g. alcohol, tobacco, drugs, etc
Pain	Aberrant reinnervation in many pelvic organs causes pain or "allodyniae" (light touch causing pain or discomfort)
Storage of pain by the CNS	Even when the injured organ is removed the pain may persist or recur; e.g. post-hysterectomy pain
Vascular effects	Injuries to vasomotor nerves are associated with hyperplasia of the vessel walls that promotes ischaemia and thrombosis e.g. preeclampsia
?Malignant change	Disruption of the autonomic nervous system together with exposure to an external mitogenic agent may result in the development of some cancers

patterns of excessive uterine activity in labour associated with administration of oxytocin and prostaglandins may result in disruption of the nerves at the endometrial-myometrial interface resulting in later hysterectomy for painful adenomyosis, or, reinnervation of the uterosacral ligaments resulting in chronic pelvic pain [10,11].

Persistent physical efforts during defaecation are endemic in Western populations (20–30%, [12]). One per cent of women only achieve defaecation once per week; three per thousand once per month! WA Lane first identified the physical signs of "chronic intestinal stasis" in the abdomen and its role in many diseases [13,14]. DP Burkitt added fibre to our breakfast tables by recognising that stool weights and oro-anal transit times differed between African and European populations [15,16]. K.W. Heaton contributed the Bristol stool chart and an important survey of East Bristol's bowel habits [12,17]. However, the key observation is that persistent physical efforts during defaecation cause injuries to pelvic autonomic nerves with abnormal neuro-immunohistochemistry in every pelvic organ demonstrating large numbers of perivascular nerves encircling small arterioles (Fig. 1d, 18). Many Western diseases show clear evidence of unexplained loss of nerves (denervation) and subsequent regrowth of nerves (reinnervation) in the affected organ [3,5]. There is a clear lineage for the proposition that the subset of "constipation" associated with persistent physical efforts during defaecation, contribute to many patterns of Western diseases over the past century (Lane–Burkitt–Heaton), with supporting clinical and epidemiological evidence that now extends to specific neuroimmunohistochemistry [18].

Consequences of injuries to uterine nerves (Table 2)

Injuries to autonomic nerves at any site in the body have wide-ranging and unpredictable consequences that depend on the relationship between the nerves and the organ, their central and peripheral neuroanatomy, and, the site, nature and extent of the neural injury ([3,5] Table 2). Some of these consequences are exaggerated in the lower genital tract where oestrogen-sensitive organs are susceptible to marked changes in size and shape. Injuries to autonomic nerves result in changes in visceral form and function, sensitivity to infection and tobacco, pain and CNS "storage" of that pain. Any breach of the integrity of the autonomic nervous system may result in non-specific symptoms such as headache, nausea, vomiting, dizziness, fatigue, etc. Similar consequences may occur in a wide range of other organs leading to diverse and varying clinical presentations of many Western diseases. The two specific lesions that occur in all pelvic organs include traumatic microneuromas and perivascular nerve fibre proliferation.

(a) Traumatic microneuromas: Traumatic injury to a nerve bundle causes major metabolic activity in the proximal stump of the nerve bundle prior to fhaotic, proliferation of abnormal, new, "nerve-lets" leading to a cone of abnormal new nerves ("traumatic microneuroma" Fig. 1b). When sufficiently established (after a number of years) touching this microneuroma causes pain or discomfort ("allodynia"). In the female pelvis there are a number of sources of "light touch"; commonly it is dilating blood vessels associated with increases in oestrogen-driven, pelvic blood flow that impinge on these microneuromas causing pain.

(b) Perivascular nerve fibre proliferation (PVNFP): Stretching a nerve bundle causes significant injuries to the nerve bundle with proliferation of abnormal, new "nerve-lets" that maintain a close relationship with the adventitia of the adjacent arteriole in the neurovascular bundle (Fig. 1c and d). Injuries to vasomotor nerves in the neurovascular bundle results in release of cytokines that also cause hyperplasia of the tunica media and intima of the (now-denervated) arteriole with narrowing of the lumen of the vessel. So there are proliferative changes in both the nerves and blood vessels. The vascular hyperplasia is identical to the Dixon–Robertson–Brosens lesion (DRB), initially described by Dixon and Robertson in their placental bed biopsy series in pre-eclampsia ([19], Fig.1c and d). They described it as a "degenerative arteriolitis" that degenerates into "fibrinoid necrosis" or "acute atherosis". In pregnancy there is elongation of blood vessels but there is no elongation of uterine nerves leading to a relative denervation of the myometrium [20]. Our group has described a similar lesion in stage IV endometriosis, chronic pelvic pain, vulvodynia, interstitial cystitis, urethral syndrome, vaginal pain, etc [7,8,18]. There are similar lesions in the uterus, cervix, Fallopian tubes and uterosacral ligaments [8].

Gynaecological conditions

There are three pathological conditions specific to gynaecology; endometriosis, adenomyosis and leiomyomas. All have neurological features, and, all may result from injuries to autonomic nerves [11,21,22]. Deposits of ectopic endometrium ("endometriosis") are largely irrelevant to clinical symptoms. In the "autonomic denervation" view these symptoms and manifestations of disease result from injuries to pelvic autonomic nerves. Injuries to myometrial and tubal nerves enable retrograde menstruation and regurgitated endometrium adheres to areas of peritoneal injury (if they are present). Advanced nulliparous "endometriosis" frequently results from progressive straining during defaecation whilst minor "endometriosis" in multiparous women may be equally painful though the laparoscopic features are relatively minor [8]. Both result from injuries to uterotubal nerves caused by injuries during childbirth, or, medical or surgical evacuation of the uterus.

Adenomyosis describes endometrium invading the myometrium; it presents in two distinct forms. In China, multiple, late, surgical or medical terminations of pregnancies result in avulsions

of the uterosacral ligaments from their insertions near the vaginal vault [8]. These injuries destroy the nerves supplying the plexus at the endometrial-myometrial interface enabling endometrium to invade the myometrium that results in huge, painless uteri that require hysterectomy at uterine weights of 250–1000 g. In Western countries women present with "painful" adenomyosis at uterine weights of 100–250 g where there has been an injury to the nerves at the endometrial-myometrial plexus i.e. within the uterus. In these uteri there is evidence of aberrant reinnervation of nerves at the endometrial-myometrial interface [11]. That may result from excessive uterine activity associated with the administration of prostaglandins or oxytocin in labour, or, over-vigorous curettage. Incremental regimens of intravenous oxytocin may contribute to increasing rates of dysfunctional labour, epidemic rates of postpartum haemorrhage (some units have experienced increases of 500% and 1000% in the rates of 1000 and 2000 ml PPH respectively over the past ten years), and, the remote consequence of painful adenomyosis some 10–15 years later

Leiomyoma are localised proliferations of myometrium; they may contain nerves, or, they may have no nerves. The latter are most common and may result from intramyometrial injuries in labour [22]. Animal models that produce denervated leiomyomas (and adenomyosis) from specific injuries to nerves at different anatomical sites may be helpful in confirming the aetiology of both pathological conditions.

All the clinical syndromes labelled in Greek also show evidence of traumatic microneuromas and perivascular nerve fibre proliferation i.e. vulvodynia, dyspareunia, dysmenorrhea, menorrhagia, etc and there are PVNFP in the Fallopian tube in some forms of ectopic pregnancy, and, uterosacral ligaments in painless adenomyosis [3]. That is not to say that every cause of a symptom e.g. vulvodynia, has a neurological origin but a significant proportion of cases will result from difficult second stages of labour, or, persistent physical efforts during defaecation. Nevertheless it identifies the pathophysiology of the majority of clinical cases enabling further questions to identify the cause of symptoms in the minority of cases.

The "great obstetric syndromes

G.J. Sophian originally described the uterorenal "reflex" in preeclampsia in a series of experiments in the 1950's [23]. Distending balloons in rabbit uteri caused immediate blanching of the renal cortex with the development of hypertension and proteinuria that we recognise as preeclampsia. Dividing the nerves between the uterus and kidneys abolishes this "reflex". In writing up his observations, Sophian believed that "resistance to myometrial stretch" may be the best description of the afferent receptor mechanism [23,24]. Having identified injured myometrial nerves and injured periarteriolar nerves (with thickened vessel walls), the "autonomic denervation" view suggests that stretching these injured nerves may be the primary afferent mechanism most likely to account for the "early" and "late-onset" pre-eclamptic syndromes respectively [24]. The remaining "great" obstetric syndromes include intrauterine growth retardation, placental abruption and preterm labour. Injuries to the nerves between the uterus and kidneys may result in intra-uterine growth retardation without hypertension. Whilst injuries to these already-injured blood vessels may account for placental abruption. Denervation of the lower genital tract may account for the many opportunist infections that account for increasing contemporary rates of preterm labour.

Autonomic connections between the uterus, kidneys, liver and heart may account for varying clinical presentations of preeclampsia, HELLP syndrome, obstetric cholestasis, and, unexplained peripartum tachycardias, whilst, injured pelvic nerves account for large numbers of clinical presentations of parous abdominal pain in subsequent pregnancies that are frequently labelled as "symphysis-pubis dysfunction" [25].

Conclusions

The simple, though profound, conclusion of these observations is that many obstetric and gynaecological syndromes may be the consequences of injuries to pelvic autonomic nerves that vary with the anatomical site, physical extent and nature of the injury. This pathophysiological approach displaces the empirical labelling of many conditions with Greek and Latin terms that imply different aetiologies e.g. vulvodynia, dyspareunia, dysmenorrhea, menorrhagia, preeclampsia, abruption, IUGR, preterm labour etc. These neural injuries result from difficult first labours, persistent physical efforts during defaecation and, medical and surgical techniques to empty the uterus. In the UK, the conduct of a woman's first labour sets the trajectory of her reproductive health for the rest of her life whereas in China, a woman's recurrent evacuations of her uterus set the trajectory for her reproductive career. This hypothesis describes an aetiological framework for much of reproductive ill-health; there is a great deal of work to supply colour and texture to these views.

Conflict of interest

None.

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